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(54) Title: EMULSION COMPOSITIONS FOR POLYFUNCTIONAL ACTIVE INGREDIENTS

(57) Abstract: The present invention provides pharmaceutical oil-in-water emulsions for delivery of polyfunctional active ingredi-  
ents. The emulsions include an aqueous phase, an emulsifier, and an oil phase, wherein the oil phase includes a structured triglyceride  
that is substantially free of triglycerides having three C<sub>6</sub>-C<sub>12</sub> fatty acid moieties, or a combination of a long chain triglyceride and a  
polarity-enhancing polarity modifier. The present invention also provides methods of treating an animal with a polyfunctional active  
ingredient, using dosage forms of the pharmaceutical emulsions.

## EMULSION COMPOSITIONS FOR POLYFUNCTIONAL ACTIVE INGREDIENTS

### FIELD OF THE INVENTION

The present invention relates to pharmaceutical delivery systems, and in particular to oil-in-water pharmaceutical emulsions for the improved delivery of polyfunctional active ingredients, such as pharmaceuticals, cosmeceuticals, nutritive agents, and diagnostic agents.

### BACKGROUND

Polyfunctional active ingredients, *i.e.*, active ingredients having at least some polar functionality, present difficult problems in formulating such compounds for effective administration to patients. A well-designed formulation should, at a minimum, be capable of presenting a therapeutically effective amount of the polyfunctional compound to the desired site of action, in a bioavailable form. Particularly when the polyfunctional active ingredient is hydrophobic, this minimal functionality has proven difficult to achieve. Delivery of a polyfunctional hydrophobic active ingredient requires interaction with aqueous physiological environments, such as blood, gastric fluids and intestinal fluids. Pharmaceutical compositions for delivery of such polyfunctional hydrophobic active ingredients should preferably carry the active ingredient through the aqueous environment, while maintaining the active ingredient compound in a bioavailable form, and avoiding or substantially reducing the use of physiologically harmful solvents or excipients.

A number of approaches to formulating polyfunctional hydrophobic active ingredients for oral or parenteral delivery are known. Several commercial formulations are available for parenteral dosage forms of polyfunctional active ingredients, based on organic cosolvent and/or synthetic surfactant solvent systems. For example, cyclosporin A (SANDIMMUNE®), paclitaxel (TAXOL®) and etoposide (VePesid®) are all commercially

1 available in injectable dosage forms containing organic solvents and/or synthetic hydrophilic  
2 surfactants. *See, Physician's Desk Reference*, Medical Economics Co. (1999).

3 Solvent/hydrophilic surfactant formulations, however, suffer from a number of  
4 serious disadvantages. Hydrophilic polyethoxylated surfactants commonly used in such  
5 formulations, such as Cremophor® and Tween®, have a high toxicity potential. Pain at the  
6 injection site, thrombophlebitis, tissue necrosis and hypersensitivity reactions are commonly  
7 observed side effects of such formulations. Cremophor EL, for example, currently used in  
8 parenteral formulations of cyclosporin, paclitaxel and teniposide, has been found to be  
9 associated with severe anaphylactic/hypersensitive reactions. Cremophor EL has also been  
10 implicated at least partially responsible in the most significant side effect of cyclosporin  
11 concentrate for injection, acute nephrotoxicity. Besides being irritating and hemolytic, such  
12 formulations are potentially subject to active precipitation during storage, upon admixing  
13 prior to administration, or upon parenteral administration, leading to further safety  
14 challenges. In addition, some hydrophilic polyethoxylated surfactants, such as Cremophor  
15 EL, cause phthalate stripping and are incompatible with commonly used plasticized PVC  
16 infusion devices.

17 As an alternative to hydrophilic surfactant/cosolvent systems, oil-in-water ("o/w")  
18 emulsion formulations have been used in polyfunctional hydrophobic active ingredient  
19 delivery. These formulations typically contain a long chain triglyceride oil phase dispersed  
20 in water and stabilized by an emulsifier layer of a phosphatide, such as soy or egg lecithin.  
21 Propofol, for example, is available commercially as Diprivan®, an o/w emulsion  
22 formulation using long chain triglycerides contained in vegetable oils, and an emulsifying  
23 agent. While such formulations may overcome some of the safety liabilities of hydrophilic  
24 surfactant/solvent based systems, the oil component may not be appropriately polar to

1 effectively incorporate polyfunctional active ingredients at desirable therapeutic levels,  
2 without compromising product safety.

3 In an attempt to improve drug loading capacity in emulsions, some approaches  
4 incorporate additional stabilizers, or include undesirably high levels of compounds which  
5 hydrolyze to form medium chain fatty acids. Such approaches, however, present problems  
6 in processing, stability, and safety.

7 Several formulations have been developed based on medium chain triglyceride  
8 ("MCT") oil phases, rather than (or in addition to) the more traditional long chain  
9 triglyceride ("LCT") oil phases. U.S. Patent No. 5,660,858 to Parikh et al. discloses  
10 cyclosporin oil-in-water emulsions with a synthetic MCT having predominantly C<sub>8</sub>-C<sub>12</sub> fatty  
11 acid chains. U.S. Patent No. 5,364,632 to Benita et al. discloses an oil-in-water emulsion of  
12 a lipophilic drug having an MCT oil carrier and a combination of ionic and non-ionic  
13 surfactants.

14 Reportedly, such formulations enable better solubilization of polyfunctional active  
15 ingredients, compared to the less polar long chain triglycerides. *See, e.g.,* Velazquez et al.,  
16 "The scientific rationale and clinical application of short-chain fatty acids and medium-chain  
17 triglycerides," *Proceedings of the Nutrition Society*, 55:49-78 (1996). However, the  
18 presence of predominantly medium chain (*i.e.*, having fatty acids with carbon chain lengths  
19 of six to ten carbon atoms) triglycerides of higher polarity in the oil phase presents  
20 significant safety and stability issues that could limit the shelf life of MCT-based  
21 formulations, or place safety limits on the infusion rate. *See, Velazquez et al., ibid,* and Van  
22 de Velde et al., "Comparative hemodynamic effects of three different parenterally  
23 administered lipid emulsions in conscious dogs," *Crit. Care Med.*, 26:132-137 (1998).

24

1       The adverse effects of parenteral MCT-based emulsions reported in animals include  
2 poor growth and nitrogen balance, and increased energy expenditure. Some reports have  
3 indicated that medium chain triglycerides may not spare protein catabolism as well as do  
4 long chain triglycerides. More importantly, MCT-based emulsions do not seem to be well-  
5 tolerated by patients. Moderate to severe side effects have been reported, such as  
6 neurotoxicity, emesis, somnolence, coma, narcosis, essential fatty acid deficiency, and  
7 ketosis in susceptible patients. Since physical mixing of MCTs and LCTs does not alter the  
8 subsequent clearance kinetics, the corresponding triacyl glycerols are cleared from the blood  
9 and oxidized unaffected in the mixture. As a result, very rapid hydrolysis of MCTs and  
10 rapid uptake of the medium chain fatty acid hydrolysis products have been observed even in  
11 a one-to-one mixture of MCTs and LCTs administered parenterally. Some of the reported  
12 side effects have been attributed to uncoupling of oxidative phosphorylation resulting from  
13 the uncontrolled entry of medium chain fatty acids into the mitochondria, due to the rapid  
14 hydrolysis of MCTs.

15       As a specific example, caprylic acid, the hydrolysis product of an MCT containing  
16 the caprylic acid ester moiety, has been demonstrated to have neurological side effects.  
17 Caprylic acid infusion simultaneously produced alterations in the sodium-potassium-  
18 adenosinetriphosphatase activity in brain tissue, and resulted in hyperventilation, coma,  
19 seizure, hypotonia and electroencephalographic changes in rabbits. (Velazquez et al.,  
20 *Proceedings of the Nutrition Society*, 55:49-78 (1996)). These events coincide with  
21 hemodynamic events, such as a decrease in cardiac output, stroke volume, and myocardial  
22 wall-thickening fraction, and an increase in aortic blood pressure and systemic vascular  
23 resistance when an MCT/LCT mixture is infused parentally in dogs. (Van de Velde et al.,  
24 *Crit. Care Med.*, 26:132-137 (1998)). Thus, medium chain triglycerides and medium-chain-

1 containing additives, such as medium chain mono- or diglycerides, which hydrolyze to  
2 medium chain fatty acids, present potentially severe safety problems in pharmaceutical  
3 emulsions.

4 Thus, there is a need for safe and effective pharmaceutical formulations of  
5 polyfunctional active ingredients that do not suffer from the foregoing disadvantages.

#### 6 7 SUMMARY OF THE INVENTION

8 It is an object of the invention to provide pharmaceutical delivery systems capable of  
9 delivering polyfunctional active ingredients.

10 It is another object of the invention to provide pharmaceutical emulsions for delivery  
11 of polyfunctional active ingredients with improved loading capacity.

12 It is another object of the invention to provide pharmaceutical emulsions for delivery  
13 of polyfunctional active ingredients that are substantially free of toxic hydrophilic  
14 surfactants.

15 It is another object of the invention to provide pharmaceutical emulsions for delivery  
16 of polyfunctional active ingredients which reduce irritation and local toxicity at the site of  
17 administration.

18 It is another object of the invention to provide pharmaceutical emulsions for delivery  
19 of polyfunctional active ingredients which overcome drug precipitation upon administration.

20 It is another object of the invention to provide pharmaceutical emulsions for delivery  
21 of polyfunctional active ingredients with fewer side effects associated with medium chain  
22 triglycerides or their hydrolysis products.

23 It is another object of the invention to provide pharmaceutical emulsions for delivery  
24 of polyfunctional active ingredients with enhanced stability.

1       It is another object of the invention to provide safer and more effective methods of  
2 treatment with polyfunctional active ingredients.

3       In accordance with these and other objects, the present invention provides  
4 pharmaceutical emulsions and methods utilizing the emulsions, to provide improved  
5 delivery of polyfunctional active ingredients. The pharmaceutical emulsions of the present  
6 invention include an aqueous phase, an oil phase, and an emulsifier, wherein the oil phase  
7 includes components chosen to increase the polarity of the oil phase, without introducing  
8 into the emulsion excessive amounts of organic solvents, hydrophilic surfactants, or  
9 compounds which include or hydrolyze to form medium chain fatty acids.

10       In one embodiment, the present invention provides a pharmaceutical emulsion for  
11 delivery of a polyfunctional active ingredient, the emulsion including an aqueous phase, an  
12 emulsifier, and a polar oil phase containing one or more structured triglycerides. The  
13 structured triglyceride can include both medium and long chain fatty acids, and is preferably  
14 free of triglycerides having three medium chain fatty acid moieties. Optionally, the  
15 composition can include additional components, such as a polyfunctional active ingredient, a  
16 long chain triglyceride, a polarity modifier, ingredients to facilitate formulation stability and  
17 patient acceptability, and processing aids.

18       In another embodiment, the present invention provides a pharmaceutical emulsion  
19 for delivery of a polyfunctional active ingredient, the emulsion including an aqueous phase,  
20 an emulsifier, and an oil phase containing a long chain triglyceride and at least one  
21 compound selected from the group consisting of acids; bases; monoglycerides; diglycerides;  
22 mixtures of mono- and diglycerides; mixtures of mono-, di- and triglycerides, acetylated  
23 monoglycerides; acetylated diglycerides; bile acids; cholesterol; cholesterol fatty acid esters;  
24 fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives of mono/diglycerides; lower

1 alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol  
2 alkyl ethers; lipophilic reaction mixtures of polyols and at least one member of the group  
3 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols;  
4 sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated alkyl ethers; and  
5 polyethoxylated sterols. Optionally, the composition can include additional components,  
6 such as a polyfunctional active ingredient, a structured triglyceride, a mono- or diglyceride,  
7 an acid or base, ingredients to facilitate formulation stability and patient acceptability, and  
8 processing aids.

9 In another embodiment, the present invention provides a pharmaceutical emulsion  
10 for delivery of a polyfunctional active ingredient, the emulsion including an aqueous phase,  
11 an emulsifier, and an oil phase containing a long chain triglyceride and a monoglyceride, a  
12 diglyceride, a mixture of mono- and diglycerides, or a mixture of mono-, di- and  
13 triglycerides. Optionally, the composition can include additional components, such as a  
14 polyfunctional active ingredient, a structured triglyceride, a polarity modifier, ingredients to  
15 facilitate formulation stability and patient acceptability, and processing aids.

16 In another embodiment, the present invention provides a pharmaceutical emulsion  
17 for delivery of a polyfunctional active ingredient, the emulsion including an aqueous phase,  
18 an emulsifier, and an oil phase containing a long chain triglyceride and an acetylated  
19 monoglyceride, an acetylated diglyceride, or a mixture thereof. Optionally, the composition  
20 can include additional components, such as a polyfunctional active ingredient, a structured  
21 triglyceride, a polarity modifier, ingredients to facilitate formulation stability and patient  
22 acceptability, and processing aids.

23 In another embodiment, the present invention provides dosage forms of the  
24 pharmaceutical emulsions.



1        In another aspect, the present invention relates to methods of using the  
2 pharmaceutical emulsions to treat patients with a polyfunctional active ingredient.

3        In another aspect, the present invention relates to methods of treating a patient with a  
4 pharmaceutical composition, wherein the composition includes effective amounts of an oil  
5 phase and an emulsifier. The amounts and components of the oil phase and emulsifier are  
6 effective to minimize drug precipitation upon administration, irritation and local toxicity at  
7 the site of administration; to alter drug biodistribution and clearance; and to minimize  
8 systemic drug toxicity, multi-drug resistance, intra-subject performance variability and/or  
9 inter-subject performance variability.

10       These and other objects and features of the present invention will become more fully  
11 apparent from the following description and appended claims, or may be learned by the  
12 practice of the invention as set forth hereinafter.

#### 14       **DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS**

15       The present invention provides pharmaceutical emulsions and methods utilizing the  
16 emulsions, to provide improved delivery of polyfunctional active ingredients, particularly  
17 hydrophobic polyfunctional active ingredients. Unlike conventional formulations, the  
18 pharmaceutical emulsions of the present invention achieve effective and stable solubilization  
19 of the polyfunctional active ingredient without excessive amounts of organic solvents,  
20 hydrophilic synthetic surfactants, or medium chain fatty acid containing compounds, such as  
21 medium chain triglycerides. The pharmaceutical emulsions of the present invention include  
22 an aqueous phase, an oil phase, and an emulsifier, wherein the oil phase includes safe and  
23 effective components chosen to increase the polarity of the oil phase, while maintaining  
24 formulation safety and stability.

1 In one embodiment, the oil phase includes a structured triglyceride. The term  
 2 "structured triglyceride" as used herein means a triglyceride, or a mixture of triglycerides, of  
 3 synthetic or natural origin, having a fatty acid chain composition including both medium  
 4 chain fatty acids and long chain fatty acids. Conventional oils, such as vegetable oils, are  
 5 primarily composed of triglycerides of long chain fatty acids. In contrast, MCT oils are  
 6 synthetic oils primarily composed of triglycerides of C<sub>8</sub>-C<sub>10</sub> fatty acids. As used herein, the  
 7 term "medium chain fatty acid" means a saturated or unsaturated fatty acid having a carbon  
 8 chain length of 6 to 12 carbon atoms, whereas the term "long chain fatty acid" means a  
 9 saturated or unsaturated fatty acid having a carbon chain length of greater than 12 carbon  
 10 atoms. Typical long chain and medium chain triglycerides can be characterized by their  
 11 fatty acid content, reported in one literature source as follows:

12 Fatty Acid	Soybean Oil	Safflower Oil	MCT Oil
13 C6			< 2%
14 C8			70%
15 C10			30%
16 C12			< 2%
17 C14	0.1 %	0.1%	
18 C16	10.5%	6.7%	
19 C18	88.5%	93.1%	
20 C20	1.1%	1.0%	

21 (Babayan, *Lipids*, 22(6):417-420 (1987); different degrees of saturation combined).

22 In contrast to both medium chain and long chain triglycerides, structured  
 23 triglycerides include both medium chain and long chain fatty acid groups. Structured  
 24 triglycerides are typically synthetically produced, and are typically a mixture of triglycerides  
 having predominantly medium and long chain fatty acid groups. An example of

commercially available structured triglycerides is the Captex 810 series (Abitec), which is reported to have the following fatty acid distribution:

Fatty Acid Chain Distribution	810A	810B	810C	810D
3 medium	62	39	15	3
2 medium 1 long	32	43	40	20
1 medium 2 long	6	16	27	44
3 long	< 1	2	3	34

(Babayan, *ibid.*) In order to avoid the adverse effects of MCT oils and their hydrolysis products, preferably the structured triglyceride does not contain significant amounts of triglycerides having three medium chain fatty acid groups. Thus, preferred structured triglycerides are those which are substantially free of MCTs, such as Captex 810D. Alternatively, fractions of Captex 810A or similar compositions which are substantially free of triglycerides having three medium chain fatty acid groups, obtained by appropriate procedures, are also suitable for use in the emulsion compositions of the present invention.

Structured triglycerides can be produced by various methods known in the art, including hydrolysis and esterification; interesterification; traditional chemical reaction sequences; lipase interesterification; genetic manipulation; or other methods, as appropriate.

Mixtures of long chain triglycerides and structured triglycerides are also within the scope of the present invention. In this embodiment, the oil phase can further include one or more oils having long chain triglycerides, such as vegetable oils, fish oils, animal fats, hydrogenated vegetable oils, partially hydrogenated vegetable oils, semi-synthetic triglycerides, synthetic triglycerides, or mixtures thereof. Fractionated, refined or purified oils of these types can also be used.

1           Specific examples of suitable long chain triglyceride-containing oils suitable for use  
2 in the compositions of the present invention include almond oil; babassu oil; borage oil;  
3 black currant seed oil; canola oil; castor oil; coconut oil; corn oil; cottonseed oil; emu oil;  
4 evening primrose oil; flax seed oil; grapeseed oil; groundnut oil; mustard seed oil; olive oil;  
5 palm oil; palm kernel oil; peanut oil; rapeseed oil; safflower oil; sesame oil; shark liver oil;  
6 soybean oil; sunflower oil; hydrogenated castor oil; hydrogenated coconut oil; hydrogenated  
7 palm oil; hydrogenated soybean oil; hydrogenated vegetable oil; a mixture of hydrogenated  
8 cottonseed oil and hydrogenated castor oil; partially hydrogenated soybean oil; a mixture of  
9 partially hydrogenated soybean oil and partially hydrogenated cottonseed oil; glyceryl  
10 trioleate; glyceryl trilinoleate; glyceryl trilinolenate; a  $\Omega 3$  polyunsaturated fatty acid  
11 triglyceride containing oil; and mixtures thereof.

12           Preferred long chain triglyceride containing oils include coconut oil; corn oil; olive  
13 oil; palm oil; peanut oil; safflower oil; sesame oil; soybean oil; hydrogenated castor oil;  
14 hydrogenated coconut oil; partially hydrogenated soybean oil; glyceryl trioleate; glyceryl  
15 trilinoleate; glyceryl trilinolenate; a  $\Omega 3$  polyunsaturated fatty acid triglyceride containing  
16 oil; and mixtures thereof.

17           More preferred long chain triglyceride containing oils include corn oil; olive oil;  
18 palm oil; peanut oil; safflower oil; sesame oil; soybean oil; hydrogenated castor oil; partially  
19 hydrogenated soybean oil; glyceryl trioleate; glyceryl trilinoleate; a  $\Omega 3$  polyunsaturated  
20 fatty acid triglyceride containing oil; and mixtures thereof.

21           The oil phase can further include one or more polarity modifiers. Without wishing to  
22 be bound by theory, it is believed that these polarity modifiers can act as polarity enhancers,  
23 to assist in adjusting the polarity of the oil phase to maximize the beneficial properties of the  
24 present emulsions. The polarity modifier is a compound or a mixture of compounds,

1 capable of modifying the interaction between the polyfunctional active ingredient and the oil  
2 phase by serving as a bridge to reduce the effects of the gap in polarity between the active  
3 ingredient and the oil.

4 Without wishing to be bound by theory, it is believed that the presence of a polarity  
5 modifier in the oil phase creates a more favorable environment for a polyfunctional active  
6 ingredient through interaction with the polarity modifier. These interactions may include  
7 hydrogen bonds, ion-dipole interactions, ion-induced dipole interactions, electrostatic  
8 interactions, and van der Waals forces, including dipole-dipole interactions (also known as  
9 Keesom forces), dipole-induced-dipole interactions (also known as Debye forces), and  
10 induced dipole-induced dipole interactions (also known as London dispersion forces).

11 These interactions can be in such a way that the incorporation of the polyfunctional  
12 active into the emulsion formulation is facilitated, or the behavior of the active upon  
13 administration is augmented in the presence of the emulsion formulation.

14 Suitable polarity modifiers include acids; bases; monoglycerides; diglycerides;  
15 mixtures of mono- and diglycerides; mixtures of mono-, di- and triglycerides; acetylated  
16 monoglycerides; acetylated diglycerides; bile acids; cholesterol; cholesterol fatty acid esters;  
17 fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives of mono/diglycerides; lower  
18 alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol  
19 alkyl ethers; sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated alkyl ethers;  
20 polyethoxylated sterols; and mixtures thereof.

21 Other suitable polarity modifiers include lipophilic reaction mixtures, or  
22 purified/fractionated lipophilic reaction mixtures, of polyols and fatty acids, glycerides,  
23 vegetable oils, hydrogenated vegetable oils, or sterols. The glyceride can be a  
24 monoglyceride, a diglyceride, a triglyceride, or a mixture thereof.

1       It will be apparent to those skilled in the art that the term "lipophilic" means those  
2 members of the foregoing groups or classes of compounds which have significant solubility  
3 in oily solvents, and poor solubility in aqueous solvents. For compounds that can be  
4 characterized by a hydrophilic-lipophilic balance ("HLB") number, such as non-ionic  
5 compounds, lipophilic compounds are generally those having an HLB value of less than  
6 about 10.

7       A preferred lipophilic reaction mixture is the reaction mixture of a transesterification  
8 reaction of a polyol and a fatty acid, a glyceride, a vegetable oil, a hydrogenated vegetable  
9 oil, a sterol, or a mixture thereof.

10       Preferred lipophilic reaction mixtures are those in which the polyol reactant is a  
11 polyhydric aliphatic alcohol, such as pentaerythritol, ethylene glycol, polyethylene glycol,  
12 propylene glycol, polypropylene glycol, sorbitol, glycerol, polyglycerol, a saccharide, a  
13 cyclodextrin, a synthetic polyhydric polymer, or a mixture thereof.

14       Preferred polarity modifiers include monoglycerides; diglycerides; mixtures of  
15 mono- and diglycerides; mixtures of mono-, di- and triglycerides; acetylated  
16 monoglycerides; acetylated diglycerides; cholesterol fatty acid esters; lower alcohol fatty  
17 acid esters; propylene glycol fatty acid esters; polyol fatty acid esters; sorbitan fatty acid  
18 esters; polyethoxylated esters; polyethoxylated sterols; lipophilic reaction mixtures of  
19 polyols and fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols;  
20 and mixtures thereof.

21       Particularly preferred polarity modifiers are monoglycerides, diglycerides, mixtures  
22 of mono- and diglycerides. The monoglycerides and diglycerides preferably have fatty acids  
23 with carbon chain lengths of greater than 10 carbon atoms.

1       Also particularly preferred are acetylated monoglycerides, acetylated diglycerides,  
2 and mixtures thereof.

3       Other particularly preferred polarity modifiers include sorbitan fatty acid esters;  
4 polyethoxylated esters; polyethoxylated sterols; lipophilic reaction mixtures of polyols and  
5 at least one member of the group consisting of fatty acids, glycerides, vegetable oils,  
6 hydrogenated vegetable oils, and sterols; and mixtures thereof.

7       Still other preferred polarity modifiers include polyethoxylated esters, such as  
8 polyethoxylated monoglycerides, polyethoxylated diglycerides, polyethoxylated  
9 triglycerides, polyethoxylated bile acids, polyethoxylated cholesterol, polyethoxylated fatty  
10 acids, polyethoxylated propylene glycol esters, polyethoxylated vegetable oils.  
11 polyethoxylated hydrogenated vegetable oils, polyethoxylated sorbitan fatty acid esters, and  
12 mixtures thereof.

13       Suitable acids and bases are pharmaceutically acceptable acids and bases, preferably  
14 those which are oil-miscible, or which can interact with the polyfunctional active ingredient  
15 to bring the active and/or the acid or base into the oil phase. The acid can be an inorganic  
16 acid, an aliphatic acid, an aromatic acid, an acidic salt, or a mixture thereof. Examples of  
17 suitable acids include hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid,  
18 carbonic acid, nitric acid, boric acid, phosphoric acid, acetic acid, acrylic acid, adipic acid,  
19 alginic acid, alkanesulfonic acid, an amino acid, ascorbic acid, benzoic acid, boric acid,  
20 butyric acid, carbonic acid, cinnamic acid, citric acid, fatty acids, formic acid, fumaric acid,  
21 gluconic acid, hydroquinosulfonic acid, hydroxybenzoic acid, isoascorbic acid, lactic acid,  
22 maleic acid, methanesulfonic acid, oxalic acid, para-bromophenylsulfonic acid, propionic  
23 acid, p-toluenesulfonic acid, salicylic acid, stearic acid, succinic acid, tannic acid, tartaric  
24

1 acid, thioglycolic acid, toluenesulfonic acid, uric acid, acidic salts of pharmaceutically  
2 acceptable cations and anions, and mixtures thereof.

3       The base can be an inorganic base, an aliphatic base, an aromatic base, a basic salt,  
4 or a mixture thereof. Examples of suitable bases include amino acids, amino acid esters,  
5 ammonium hydroxide, potassium hydroxide, sodium hydroxide, sodium hydrogen  
6 carbonate, aluminum hydroxide, calcium carbonate, magnesium hydroxide, magnesium  
7 aluminum silicate, synthetic aluminum silicate, synthetic hydrotalcite, magnesium aluminum  
8 hydroxide, glucamine and homologs thereof, diisopropylethylamine, ethanolamine,  
9 ethylenediamine, triethanolamine, triethylamine, trihydroxyethylamine, trisopropanolamine,  
10 basic salts of pharmaceutically acceptable cations and anions, and mixtures thereof.

11       The optional acids and bases can be included in amounts sufficient to adjust the pH  
12 and/or the osmolality of the emulsion, the solubility of the polyfunctional active ingredient,  
13 the kinetic release profile, or other properties of the emulsion, as desired.

14       In order to fully realize the important safety, stability, and other advantages of the  
15 compositions of the present invention, it is preferred that the total amount of fatty acid  
16 groups of the oil phase, including free fatty acids and the fatty acid moieties of fatty acid  
17 containing compounds, having a carbon chain length of from 6 to 12 carbon atoms, be less  
18 than about 50% by weight, preferably less than about 40% by weight, and more preferably  
19 less than about 30% by weight, based on the total weight of the fatty acid groups of the oil  
20 phase. Similarly, it is preferred that the total amount of fatty acid groups of the oil phase,  
21 including free fatty acids and the fatty acid moieties of fatty acid containing compounds,  
22 having a carbon chain length of greater than 12 carbon atoms, be greater than about 10% by  
23 weight, preferably greater than about 30% by weight, and more preferably greater than about  
24 50% by weight, based on the total weight of the fatty acid groups of the oil phase.



1       The oil phase itself can be up to about 30% of the total weight of the emulsion, more  
2 typically up to about 20% of the total weight of the emulsion, and most typically up to about  
3 10% of the total weight of the emulsion.

4       The pharmaceutical emulsions of the present invention also include an emulsifier in  
5 an amount sufficient to form an oil in water emulsion. It should be appreciated that the  
6 appropriate amount of emulsifier may be different, depending upon whether or not a  
7 polyfunctional active ingredient is present in the emulsion, since some active ingredients  
8 may have self-emulsifying properties, or may become self-emulsifying after interacting with  
9 certain polarity modifiers. The emulsifier stabilizes the emulsion by increasing the  
10 mechanical bilayer strength, and/or by charge repulsion and/or steric hindrance  
11 modifications. Typically, the emulsifier will be present in an amount of less than about 20%  
12 by weight, more typically less than about 10% by weight, based on the total weight of the  
13 composition. A suitable emulsifier can be ceramide; a mixed chain phospholipid; a cationic  
14 lipid; an oligolipid; a phospholipid; a carnitine; a sphingosine; a sphingomyelin; a glycolipid;  
15 a lipoprotein; an apoprotein; an amphiphilic protein/peptide; an amphiphilic synthetic  
16 polymer; a bile salt; a fatty acid; a fatty alcohol; a fatty amine; a fatty quaternary ammonium  
17 salt; a polyethoxylated fatty acid; a polyethoxylated glyceride; a polyethoxylated  
18 phospholipid; a polyethoxylated sorbitan fatty acid ester; a polyethoxylated sterol; a  
19 polyethoxylated vegetable oil; a polyethoxylated hydrogenated vegetable oil; a reaction  
20 mixture of a polyol and at least one member of the group consisting of fatty acids,  
21 glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; a sorbitan fatty acid  
22 ester; or a mixture thereof.

23       The glyceride of the reaction mixture can be a monoglyceride, a diglyceride, a  
24 triglyceride, or a mixture thereof. The polyol of the reaction mixture is preferably a

1 polyhydric aliphatic alcohol, such as pentaerythritol, ethylene glycol, polyethylene glycol,  
2 propylene glycol, polypropylene glycol, sorbitol, glycerol, polyglycerol, a saccharide, a  
3 cyclodextrin, a synthetic polyhydric polymer, or a mixture thereof. The reaction mixture is  
4 preferably a reaction mixture of a transesterification reaction of a polyol and a fatty acid, a  
5 glycerides, a vegetable oil, a hydrogenated vegetable oil, a sterol, or a mixture thereof.

6 Preferred emulsifiers include phospholipids, such as egg phospholipids, soy  
7 phospholipids, phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines,  
8 phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, mixed chain phospholipids,  
9 lysophospholipids, hydrogenated phospholipids, partially hydrogenated phospholipids, and  
10 mixtures thereof.

11 The emulsions of the present invention can also include other additives, such as  
12 glycerol, ethanol, propylene glycol, an antioxidant, an antiseptic, a buffering agent, a  
13 chelating agent, a colorant, a flavorant, an odorant, an osmotic modifier, a preservative, a  
14 solubilizer, a solvent, a tonicifier, a trace element, a viscomodulator, or a mixture thereof.  
15 Such additional additives can be present in the oil phase, the aqueous phase, or both.

16 Preferably, the pharmaceutical emulsion includes a polyfunctional active ingredient;  
17 *i.e.*, an active ingredient having at least some polar functionality. Such active ingredients  
18 can be drugs, cosmeceuticals, nutritional agents, diagnostic agents and the like. In one  
19 embodiment, the polyfunctional active ingredient is a hydrophilic active ingredient having  
20 an octanol/water partition coefficient (*i.e.*, the ratio of its activity in octanol to its activity in  
21 water) of less than about 100, preferably less than about 10. In another embodiment, the  
22 polyfunctional active ingredient is a hydrophobic active ingredient having an *intrinsic*  
23 aqueous solubility of less than about 1 mg/mL, preferably less than about 0.1 mg/mL. Of  
24

1 course, salts, isomers, derivatives, and mixtures of polyfunctional active ingredients can also  
2 be used.

3 Polyfunctional active ingredients can be, for example, analgesics and anti-  
4 inflammatory agents, anthelmintics, anti-arrhythmic agents, anti-asthma agents, anti-  
5 bacterial agents, anti-viral agents, anti-coagulants, anti-depressants, anti-diabetics, anti-  
6 epileptics, anti-fungal agents, anti-gout agents, anti-hypertensive agents, anti-malarials, anti-  
7 migraine agents, anti-muscarinic agents, anti-neoplastic agents and immunosuppressants,  
8 anti-protozoal agents, anti-thyroid agents, anti-tussives, anxiolytic, sedatives, hypnotics and  
9 neuroleptics,  $\beta$ -Blockers, cardiac inotropic agents, corticosteroids, diuretics, anti-  
10 parkinsonian agents, gastro-intestinal agents, histamine H<sub>2</sub>-receptor antagonists, keratolytics,  
11 lipid regulating agents, muscle relaxants, anti-anginal agents, sex hormones and stimulants.  
12 The polyfunctional active ingredient can also be a cytokine, a peptidomimetic, a protein, a  
13 peptide, a toxoid, a serum, an antibody, a vaccine, a nucleoside, a nucleotide, a portion of  
14 genetic material, a nucleic acid, DNA, RNA, an oligodeoxynucleotide, or an  
15 oligonucleotide.

16 Examples of suitable polyfunctional active ingredients include acarbose; acyclovir;  
17 acetyl cysteine; acetylcholine chloride; alatrofloxacin; alendronate; alglucerase; amantadine  
18 hydrochloride; ambenonium; amifostine; amiloride hydrochloride; aminocaproic acid;  
19 amphotericin B; antihemophilic factor (human); antihemophilic factor (porcine);  
20 antihemophilic factor (recombinant); aprotinin; asparaginase; atenolol; atracurium besylate;  
21 atropine; azithromycin; aztreonam; BCG vaccine; bacitracin; becalermin; belladonna; bepridil  
22 hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon; carboplatin;  
23 capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium; cefepime  
24 hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium; cefotoxime;

1 cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalixin; cephapirin  
2 sodium; cholera vaccine; chronic gonadotropin; cidofovir; cisplatin; cladribine; clidinium  
3 bromide; clindamycin and clindamycin derivatives; ciprofloxacin; clondronate;  
4 colistimethate sodium; colistin sulfate; corticotropin; cosyntropin; cromalyn sodium;  
5 cytarabine; daltaperin sodium; danaproid; deforoxamine; denileukin diftitox; desmopressin;  
6 diatrizoate meglumine and diatrizoate sodium; dicyclomine; didanosine; dirithromycin;  
7 dopamine hydrochloride; dornase alpha; doxacurium chloride; doxorubicin; editronate  
8 disodium; elanaprilat; enkephalin; enoxacin; enoxaprin sodium; ephedrine; epinephrine;  
9 epoetin alpha; erythromycin; esmol hydrochloride; factor IX; famciclovir; fludarabine;  
10 fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor;  
11 granulocyte-macrophage stimulating factor; growth hormones- recombinant human; growth  
12 hormone- bovine; gentamycin; glucagon; glycopyrolate; gonadotropin releasing hormone  
13 and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin; hemophilus B conjugate  
14 vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin  
15 sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-  
16 human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin glargine; insulin  
17 detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; japanese  
18 encephalitis virus vaccine; lamivudine; leucovorin calcium; leuprolide acetate; levofloxacin;  
19 lincomycin and lincomycin derivatives; lobucavir; lomefloxacin; loracarbef; mannitol;  
20 measles virus vaccine; meningococcal vaccine; menotropins; mephenzolate bromide;  
21 mesalmine; methanamine; methotrexate; methscopolamine; metformin hydrochloride;  
22 metoprolol; mezocillin sodium; mivacurium chloride; mumps viral vaccine; nedocromil  
23 sodium; neostigmine bromide; neostigmine methyl sulfate; neotontin; norfloxacin;  
24 octreotide acetate; ofloxacin; olpadronate; oxytocin; pamidronate disodium; pancuronium

1 bromide; paroxetine; pefloxacin; pentamidine isethionate; pentostatin; pentoxifylline;  
2 periciclovir; pentagastrin; phentolamine mesylate; phenylalanine; physostigmine salicylate;  
3 plague vaccine; piperacillin sodium; platelet derived growth factor-human; pneumococcal  
4 vaccine polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV);  
5 polymixin B sulfate; pralidoxine chloride; pramlintide; pregabalin; propofenone;  
6 propenthaline bromide; pyridostigmine bromide; rabies vaccine; residronate; ribavarin;  
7 rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate; sincalide; small pox  
8 vaccine; solatol; somatostatin; sparfloxacin; spectinomycin; stavudine; streptokinase;  
9 streptozocin; suxamethonium chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta;  
10 ticarcillin; tiludronate; timolol; tissue type plasminogen activator; TNFR:Fc; TNK-tPA;  
11 trandolapril; trimetrexate gluconate; trospectinomycin; trovafloxacin; tubocurarine chloride;  
12 tumor necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valaciclovir;  
13 valsartan; varicella virus vaccine live; vasopressin and vasopressin derivatives; vecoronium  
14 bromide; vinblastin; vincristine; vinorelbine; vitamin B12 ; warfarin sodium; yellow fever  
15 vaccine; zalcitabine; zanamavir; zolandonate; and zidovudine.

16 Additional examples of suitable polyfunctional active ingredients include tramadol,  
17 celecoxib, etodolac, refocoxib, oxaprozin, leflunomide, diclofenac, nabumetone, acetyl  
18 coenzyme Q10, ibuprofen, flurbiprofen, tetrahydrocannabinol, capsaicin, ketorolac,  
19 albendazole, ivermectin, amiodarone, zileuton, zafirlukast, albuterol, montelukast,  
20 azithromycin, ciprofloxacin, clarithromycin, dirithromycin, rifabutine, rifapentine,  
21 trovafloxacin, baclofen, ritanovir, saquinavir, nelfinavir, efavirenz, dicoumarol, tirofibrin,  
22 cilostazol, ticlidopine, clopidrogel, oprevelkin, paroxetine, sertraline, venlafaxine,  
23 bupropion, clomipramine, miglitol, repaglinide, glymepride, pioglitazone, rosigiltazone,  
24 troglitazone, glyburide, glipizide, glibenclamide, carbamezepine, fosphenytion, tiagabine,

1 topiramate, lamotrigine, vigabatrin, amphotericin B, butenafine, terbinafine, itraconazole,  
2 flucanazole, miconazole, lycopene, ketoconazole, metronidazole, griseofulvin,  
3 nitrofurantoin, spironolactone, lisinopril, benezepril, nifedipine, nilsolidipine, telmisartan,  
4 irbesartan, eposartan, valsartan, candesartan, minoxidil, terazosin, halofantrine, mefloquine,  
5 dihydroergotamine, ergotamine, frovatriptan, pizofetin, sumatriptan, zolmitriptan,  
6 naratriptan, rizatriptan, aminogluthemide, busulphan, cyclosporine, mitoxantrone, irinotecan,  
7 etoposide, teniposide, paclitaxel, tacrolimus, sirolimus, tamoxifen, camptothecin, topotecan,  
8 nilutamide, bicalutamide, ephedrine, toremifene, atovaquone, metronidazole, furazolidone,  
9 paricalcitol, benzonatate, midazolam, zolpidem, gabapentin, zopiclone, digoxin,  
10 beclomethsone, budesonide, betamethasone, prednisolone, cisapride, cimetidine,  
11 loperamide, famotidine, lansoprazole, rabeprazole, nizatidine, omeprazole, citrizen,  
12 cinnarizine, dexchlorpheniramine, loratadine, clemastine, fexofenadine, chlorpheniramine,  
13 acutretin, tazarotene, calcipotriene, calcitriol, targretin, ergocalciferol, cholecalciferol,  
14 isotretinoin, tretinoin, calcifediol, fenofibrate, probucol, gemfibrozil, cerivastatin, pravastatin,  
15 simvastatin, fluvastatin, atorvastatin, tizanidine, dantrolene, isosorbide dinitrate, a carotene,  
16 dihydrotachysterol, vitamin A, vitamin D, vitamin E, vitamin K, an essential fatty acid  
17 source, codeine, fentanyl, methadone, nalbuphine, pentazocine, clomiphene, danazol,  
18 dihydro epiandrosterone, medroxyprogesterone, progesterone, rimexolone, megestrol  
19 acetate, osteradiol, finasteride, mefepristone, amphetamine, L-thyroxine, tamsulosin,  
20 methoxsalen, tacrine, donepezil, raloxifene, vertoporphin, sibutramine and pyridostigmine.

21 Salts, derivatives, isomers and mixtures of polyfunctional active ingredients can also  
22 be used.

23 The emulsions of the present invention can be produced by methods known in the art  
24 for forming emulsions, and examples of particular methods are shown in the Examples

1 herein. It should be understood that formulation factors such as active characteristics,  
2 packaging, excipient purity and sourcing, and processing factors, such as sequence or  
3 method of excipient/drug addition, energy input, and sterilization cycle factors affect the  
4 commercial viability or therapeutic benefit of any given emulsion product.

5       An example of a typical process is as follows: An appropriate amount of the  
6 polyfunctional active is dissolved in the desired oil phase containing the appropriate polarity  
7 modifier(s) at the desired temperature. To further increase the load of the polyfunctional  
8 active or to facilitate the process, the active can be solubilized in an appropriate solvent or  
9 mixture of solvents prior to adding active to the oil phase. The solvents used in such  
10 processes can then be partially or completely removed, depending on the tolerance of the  
11 formulation to the residual solvents. Appropriate polarity modifier can also be added to the  
12 solvent along with the active. Alternatively, in the presence of the polarity modifier, the  
13 solvent can be removed prior to mixing with the other oil components. The emulsifier, such  
14 as a phospholipid, can be dispersed in the oil phase directly, or it can be dispersed in an  
15 aqueous solution of glycerol or other tonicifier, with or without an antioxidant and with or  
16 without a preservative at the desired temperature. Chelators or bufferants can also be  
17 optionally included to improve stability of the final product.

18       The oil solution is then mixed with an aqueous solution at an appropriate  
19 temperature and for a sufficient amount of time to fully emulsify the oil. The mean diameter  
20 of the resulting coarse emulsion is preferably less than 20 microns. The resulting mixture is  
21 further homogenized at a desired pressure in batch-wise or continuous cycles until the  
22 desired particle size is obtained, typically a submicron particle size. Several high pressure  
23 homogenizers are available for this process, including EmulsiFlex (Avestin), microfluidizer  
24

1 (Microfluidics), and Rannie homogenizer (APV). The resulting emulsion can be further pH  
2 adjusted and heat-, filter-, or radiation-sterilized.

3 Of course, in embodiments which do not include a polyfunctional active ingredient,  
4 the same general procedure can be followed, omitting the active.

5 Preferred emulsions can have a mean particle diameter of less than about 5  $\mu\text{m}$ ,  
6 preferably less than about 2  $\mu\text{m}$ , more preferably less than about 1  $\mu\text{m}$ , still more preferably  
7 less than about 0.5  $\mu\text{m}$ , and most preferably less than about 0.3  $\mu\text{m}$ . Particle size can be  
8 determined by conventional methods, such as by measurement with a particle size analyzer.

9 In another embodiment, the present invention is directed to a pharmaceutical  
10 emulsion for delivery of a polyfunctional active ingredient as described above, wherein the  
11 oil phase of the emulsion includes a long chain triglyceride, and at least one compound  
12 selected from the group consisting of acids, bases, monoglycerides, diglycerides, acetylated  
13 monoglycerides; acetylated diglycerides; bile acids; cholesterol; cholesterol fatty acid esters;  
14 fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives of mono/diglycerides; lower  
15 alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol  
16 alkyl ethers; lipophilic reaction mixtures of polyols and at least one member of the group  
17 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols;  
18 sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated alkyl ethers; and  
19 polyethoxylated sterols. In this embodiment, the long chain triglyceride, the other  
20 components of the oil phase, and the emulsifier can be any of those previously described.  
21 The composition can further include a structured triglyceride, a polyfunctional active  
22 ingredient, or any of the other additives described above.

23 In another embodiment, the oil phase includes a long chain triglyceride and at least  
24 one compound selected from the group consisting of monoglycerides; diglycerides;



1 acetylated monoglycerides; acetylated diglycerides; bile acids; cholesterol; cholesterol fatty  
2 acid esters; fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives of  
3 mono/diglycerides; lower alcohol fatty acid esters; propylene glycol fatty acid esters; polyol  
4 fatty acid esters; polyol alkyl ethers; lipophilic reaction mixtures of polyols and at least one  
5 member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
6 vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated  
7 alkyl ethers; polyethoxylated sterols; and mixtures thereof. In this embodiment, the long  
8 chain triglyceride, the other components of the oil phase, and the emulsifier can be any of  
9 those previously described. The composition can further include a structured triglyceride, a  
10 polyfunctional active ingredient, or any of the other additives described above.

11 In another embodiment, the oil phase includes a long chain triglyceride and at least  
12 one compound selected from the group consisting of acids; bases; acetylated  
13 monoglycerides; acetylated diglycerides; bile acids; cholesterol; cholesterol fatty acid esters;  
14 fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives of mono/diglycerides; lower  
15 alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol  
16 alkyl ethers; lipophilic reaction mixtures of polyols and at least one member of the group  
17 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols;  
18 sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated alkyl ethers;  
19 polyethoxylated sterols; and mixtures thereof. In this embodiment, the long chain  
20 triglyceride, the other components of the oil phase, and the emulsifier can be any of those  
21 previously described. The composition can further include a structured triglyceride, a  
22 polyfunctional active ingredient, or any of the other additives described above.

23 In another embodiment, the oil phase includes a long chain triglyceride and at least  
24 one compound selected from the group consisting of acids; bases; monoglycerides;

1 diglycerides; bile acids; cholesterol; cholesterol fatty acid esters; fatty acids; fatty alcohols;  
2 fusidic acids; lactic acid derivatives of mono/diglycerides; lower alcohol fatty acid esters;  
3 propylene glycol fatty acid esters; polyol fatty acid esters; polyol alkyl ethers; lipophilic  
4 reaction mixtures of polyols and at least one member of the group consisting of fatty acids,  
5 glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty acid  
6 esters; polyethoxylated esters; polyethoxylated alkyl ethers; polyethoxylated sterols; and  
7 mixtures thereof. In this embodiment, the long chain triglyceride, the other components of  
8 the oil phase, and the emulsifier can be any of those previously described. The composition  
9 can further include a structured triglyceride, a polyfunctional active ingredient, or any of the  
10 other additives described above.

11 In another embodiment, the oil phase includes a long chain triglyceride and at least  
12 one compound selected from the group consisting of monoglycerides; diglycerides;  
13 acetylated monoglycerides; acetylated diglycerides; cholesterol fatty acid esters; fatty  
14 alcohols; lower alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid  
15 esters; lipophilic reaction mixtures of polyols and at least one member of the group  
16 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols;  
17 sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated alkyl ethers;  
18 polyethoxylated sterols; and mixtures thereof. In this embodiment, the long chain  
19 triglyceride, the other components of the oil phase, and the emulsifier can be any of those  
20 previously described. The composition can further include a structured triglyceride, a  
21 polyfunctional active ingredient, or any of the other additives described above.

22 In another embodiment, the oil phase includes a long chain triglyceride and at least  
23 one compound selected from the group consisting of acids; bases; acetylated  
24 monoglycerides; acetylated diglycerides; cholesterol fatty acid esters; fatty alcohols; lactic

1 acid derivatives of mono/diglycerides; lower alcohol fatty acid esters; propylene glycol fatty  
2 acid esters; polyol fatty acid esters; polyol alkyl ethers; lipophilic reaction mixtures of  
3 polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable  
4 oils, hydrogenated vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated  
5 esters; polyethoxylated alkyl ethers; polyethoxylated sterols; and mixtures thereof. In this  
6 embodiment, the long chain triglyceride, the other components of the oil phase, and the  
7 emulsifier can be any of those previously described. The composition can further include a  
8 structured triglyceride, a polyfunctional active ingredient, or any of the other additives  
9 described above.

10 In another embodiment, the oil phase includes a long chain triglyceride and at least  
11 one compound selected from the group consisting of acids; bases; monoglycerides;  
12 diglycerides; cholesterol fatty acid esters; fatty alcohols; fusidic acids; derivatives of  
13 mono/diglycerides; lower alcohol fatty acid esters; propylene glycol fatty acid esters; polyol  
14 fatty acid esters; polyol alkyl ethers; lipophilic reaction mixtures of polyols and at least one  
15 member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
16 vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated  
17 alkyl ethers; polyethoxylated sterols; and mixtures thereof. In this embodiment, the long  
18 chain triglyceride, the other components of the oil phase, and the emulsifier can be any of  
19 those previously described. The composition can further include a structured triglyceride, a  
20 polyfunctional active ingredient, or any of the other additives described above.

21 In another embodiment, the oil phase includes a long chain triglyceride and at least  
22 one compound selected from the group consisting of acetylated monoglycerides; acetylated  
23 diglycerides; bile acids; cholesterol; cholesterol fatty acid esters; fatty acids; fatty alcohols;  
24 fusidic acids; lactic acid derivatives of mono/diglycerides; lower alcohol fatty acid esters;

1 propylene glycol fatty acid esters; polyol fatty acid esters; polyol alkyl ethers; lipophilic  
2 reaction mixtures of polyols and at least one member of the group consisting of fatty acids,  
3 glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty acid  
4 esters; polyethoxylated esters; polyethoxylated alkyl ethers; polyethoxylated sterols; and  
5 mixtures thereof. In this embodiment, the long chain triglyceride, the other components of  
6 the oil phase, and the emulsifier can be any of those previously described. The composition  
7 can further include a structured triglyceride, a polyfunctional active ingredient, or any of the  
8 other additives described above.

9       In another embodiment, the oil phase includes a long chain triglyceride and at least  
10 one compound selected from the group consisting of monoglycerides; diglycerides; bile  
11 acids; cholesterol; cholesterol fatty acid esters; fatty acids; fatty alcohols; fusidic acids;  
12 lactic acid derivatives of mono/diglycerides; lower alcohol fatty acid esters; propylene  
13 glycol fatty acid esters; polyol fatty acid esters; polyol alkyl ethers; lipophilic reaction  
14 mixtures of polyols and at least one member of the group consisting of fatty acids,  
15 glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty acid  
16 esters; polyethoxylated esters; polyethoxylated alkyl ethers; polyethoxylated sterols; and  
17 mixtures thereof. In this embodiment, the long chain triglyceride, the other components of  
18 the oil phase, and the emulsifier can be any of those previously described. The composition  
19 can further include a structured triglyceride, a polyfunctional active ingredient, or any of the  
20 other additives described above.

21       In another embodiment, the oil phase includes a long chain triglyceride and at least  
22 one compound selected from the group consisting of acids; bases; bile acids; cholesterol;  
23 cholesterol fatty acid esters; fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives  
24 of mono/diglycerides; lower alcohol fatty acid esters; propylene glycol fatty acid esters;

1 polyol fatty acid esters; polyol alkyl ethers; lipophilic reaction mixtures of polyols and at  
2 least one member of the group consisting of fatty acids, glycerides, vegetable oils,  
3 hydrogenated vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters;  
4 polyethoxylated alkyl ethers; polyethoxylated sterols; and mixtures thereof. In this  
5 embodiment, the long chain triglyceride, the other components of the oil phase, and the  
6 emulsifier can be any of those previously described. The composition can further include a  
7 structured triglyceride, a polyfunctional active ingredient, or any of the other additives  
8 described above.

9 In another embodiment, the oil phase includes a long chain triglyceride and at least  
10 one compound selected from the group consisting of bile acids; cholesterol; cholesterol fatty  
11 acid esters; fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives of  
12 mono/diglycerides; lower alcohol fatty acid esters; propylene glycol fatty acid esters; polyol  
13 fatty acid esters; polyol alkyl ethers; lipophilic reaction mixtures of polyols and at least one  
14 member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
15 vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated  
16 alkyl ethers; polyethoxylated sterols; and mixtures thereof. In this embodiment, the long  
17 chain triglyceride, the other components of the oil phase, and the emulsifier can be any of  
18 those previously described. The composition can further include a structured triglyceride, a  
19 polyfunctional active ingredient, or any of the other additives described above.

20 In another embodiment, the oil phase includes a long chain triglyceride, and at least  
21 one compound selected from the group consisting of monoglycerides, diglycerides, mixtures  
22 of mono- and diglycerides, and mixtures of mono-, di- and triglycerides. In this  
23 embodiment, the long chain triglyceride, the other components of the oil phase, and the  
24 emulsifier can be any of those previously described. The composition can further include a

1 structured triglyceride, a polyfunctional active ingredient, or any of the other additives  
2 described above.

3 In another embodiment, the oil phase includes a long chain triglyceride, and at least  
4 one compound selected from the group consisting of acetylated monoglycerides, acetylated  
5 diglycerides, and mixtures thereof. In this embodiment, the long chain triglyceride, the  
6 other components of the oil phase, and the emulsifier can be any of those previously  
7 described. The composition can further include a structured triglyceride, a polyfunctional  
8 active ingredient, or any of the other additives described above.

9 In another embodiment, the oil phase includes a long chain triglyceride and a  
10 lipophilic reaction mixture, or a purified/fractionated lipophilic reaction mixture, of a polyol  
11 and at least one member of the group consisting of fatty acids, glycerides, vegetable oils,  
12 hydrogenated vegetable oils, and sterols. In this embodiment, the long chain triglyceride,  
13 the other components of the oil phase, and the emulsifier can be any of those previously  
14 described. The composition can further include a structured triglyceride, a polyfunctional  
15 active ingredient, or any of the other additives described above.

16 In another embodiment, the oil phase includes a long chain triglyceride and at least  
17 one compound selected from the group consisting of polyethoxylated esters, polyethoxylated  
18 alkyl ethers, polyethoxylated sterols, and mixtures thereof. In this embodiment, the long  
19 chain triglyceride, the other components of the oil phase, and the emulsifier can be any of  
20 those previously described. The composition can further include a structured triglyceride, a  
21 polyfunctional active ingredient, or any of the other additives described above.

22 In another embodiment, the present invention is directed to a pharmaceutical  
23 emulsion for delivery of a polyfunctional active ingredient as described above, wherein the  
24 oil phase of the emulsion includes a water-immiscible triglyceride, and at least one

1 pharmaceutically acceptable acid or pharmaceutically acceptable base. The water-  
2 immiscible triglyceride can be a long chain triglyceride or a structured triglyceride, and  
3 these and other components of the oil phase and the emulsifier can be any of those  
4 previously described. The composition can further include a polarity modifier, a structured  
5 triglyceride, a long chain triglyceride, a polyfunctional active ingredient, or any of the other  
6 additives described above.

7       The present invention is also directed to dosage forms of any of the pharmaceutical  
8 emulsions described herein. The dosage form can be the pharmaceutical emulsion processed  
9 by lyophilization, encapsulation, extrusion, homogenization, sonication, melting,  
10 solubilizing, evaporation, mixing, coating, size reduction, spraying, sterilization, filtration,  
11 irradiation, or a combination thereof. It should be appreciated that the ability of the  
12 pharmaceutical composition to be processed by particular processing methods may depend  
13 upon the proper choice and sequence of processing steps, as is known to those skilled in the  
14 art.

15       The dosage form can be formulated as an injectable, a drink, an eye drop or spray, a  
16 nasal drop or spray, a buccal drop or spray, a cervical drop or spray, an inhalant, a lotion, a  
17 gel, a liniment, a cream, a paste, a solution, a suppository, an ovule, a wafer, a troche, a  
18 sachet, an elixir, a tincture, a douche, an aerosol, a patch, or a combination thereof, and can  
19 be adapted for parenteral, enteral, ocular, nasal, sublingual, buccal, topical, intra-cervical,  
20 rectal, intramuscular, intra-dermal, pulmonary, transmucosal, intra-theal, intravenous, intra-  
21 arterial, epidural, intra-cavity, intra-organ transdermal, intra-lymphatic, intra-cranular, or  
22 intra-tumoral administration, or a combination thereof. *Preferred dosage forms are those*  
23 *adapted for parenteral and pulmonary administration.*

24       Preferably, the dosage form also includes a polyfunctional active ingredient,

1 although in some circumstances it may be desirable to formulate the polyfunctional active  
2 ingredient in a separate dosage form for administration to a patient prior to, concurrently  
3 with, or subsequently to, administration of the pharmaceutical emulsion. When the dosage  
4 form includes a polyfunctional active ingredient, the active ingredient can be present in a  
5 therapeutically effective amount, as determined by one skilled in the art according to the  
6 pharmacological effect of the active ingredient, the needs of the patient, and other  
7 considerations well known in the art. In addition, part of the therapeutically effective  
8 amount of the polyfunctional active ingredient can also be formulated as a separate dosage  
9 form.

10 In another aspect, the present invention is directed to methods of treating an animal  
11 with a polyfunctional active ingredient. The method includes the steps of administering to  
12 the animal a dosage form of a pharmaceutical emulsion, as described above, and a  
13 therapeutically effective amount of a polyfunctional active ingredient. The active ingredient  
14 can be present in the dosage form of the pharmaceutical emulsion, in a separate dosage  
15 form, or both. The polyfunctional active ingredient can be administered to the animal prior  
16 to, concurrently with, or subsequent to, administering the dosage form of the pharmaceutical  
17 emulsion. The animal is preferably a mammal, and more preferably a human. Suitable  
18 emulsions include any of the emulsions described above.

19 In another aspect, the present invention is directed to methods of treating a patient  
20 with a pharmaceutical composition, wherein the composition includes effective amounts of  
21 an oil phase and an emulsifier. The amounts and components of the oil phase and emulsifier  
22 are effective to minimize drug precipitation upon administration, irritation and local toxicity  
23 at the site of administration; to alter drug biodistribution and clearance; and to minimize  
24 systemic drug toxicity, multi-drug resistance, intra-subject performance variability and/or



1 inter-subject performance variability.

2 In use, the compositions and methods of the present invention provide significant  
3 advantages over conventional formulations of polyfunctional active ingredients. These  
4 advantages include:

5 1. The present compositions are free of toxic hydrophilic polyethoxylated  
6 surfactants, such as Cremophors® and Tweens®, that are traditionally used in parenteral  
7 formulations of polyfunctional hydrophobic active ingredients. By substantially reducing  
8 the need for these toxic surfactants, the present compositions eliminate potentially serious  
9 side effects associated with polyethoxylated surfactants, including potential hemolytic  
10 activity. In addition, compositions free of Cremophor EL also have the advantage of being  
11 compatible with plasticized PVC infusion devices.

12 2. Potential reduction in irritation, thrombophlebitis, and necrosis of local tissue  
13 at the injection site. Without wishing to be bound by theory, it is believed that being void of  
14 the large amount of surfactants present in the currently commercially available formulations  
15 of polyfunctional active ingredients, the present emulsion formulations can alleviate  
16 irritation, thrombophlebitis, and necrosis of local tissue at the injection site. In addition,  
17 these emulsion formulations are believed to reduce the irritation and necrosis of local tissue  
18 at the injection site caused by the direct contact with the irritating/cytotoxic actives by  
19 encapsulating the actives inside the oil phase. For hydrophobic or hydrophilic actives that  
20 are intrinsically irritating, encapsulation in emulsion droplets enables the active to overcome  
21 this limitation.

22 3. Ease of administration. Current polyethoxylated surfactant-containing  
23 formulations require dilution in 0.9% sodium chloride injection or 5% dextrose injection to  
24 different extents immediately before intravenous infusion, depending on the concentration of

1 the surfactant present in the formulations. However, for a hydrophilic surfactant-free  
2 emulsion formulation, no extra step is expected to dilute the formulation prior to  
3 administration, thus potentially reducing costs and eliminating the chance of mistakes  
4 inherent in the extra step of dilution.

5 4. Higher loading capacity for polyfunctional hydrophobic actives than long  
6 chain triglyceride-based emulsion formulations, and more stable than medium chain-based  
7 emulsions. Structured triglycerides are believed to have a higher solubilizing potential for  
8 polyfunctional hydrophobic actives than do long chain triglycerides alone. The presence of  
9 shorter chain fatty acid groups makes the structured triglyceride more polar than long chain  
10 triglycerides, but not so polar as to negatively affect drug solubility and product stability, as  
11 is believed to be the case with medium chain triglycerides. These stable, higher drug  
12 loading formulations offer more practical dosing and rates of infusions without undesirable  
13 excessive lipid and volume doping in patients. Moreover, higher drug loading present  
14 sufficient production, storage, and shipping opportunities.

15 5. Fewer side effects than MCT-based emulsion formulations. By avoiding the  
16 use of medium chain triglycerides, and minimizing the amounts of compounds which can  
17 hydrolyze to medium chain fatty acids, the adverse effects observed with parenteral MCT  
18 emulsion formulations reported in animal studies can be minimized. In addition, structured  
19 triglycerides are known to offer improved protein sparing, weight gain, N balance and  
20 hepatic and muscle protein synthesis. Structured triglycerides do not increase energy  
21 expenditure as do MCTs, nor do structured triglycerides adversely affect the RES.  
22 Presumably, these effects are due to the structured triglycerides having intermediate  
23 clearance and oxidation rates, relative to LCTs and MCTS. Since the hydrolysis of  
24 structured triglycerides is slower than that of MCTs, it is believed that the adverse

1 hemodynamic effects associated with uncontrolled excess build up of medium chain fatty  
2 acid concentrations are eliminated.

3         6.       Safer additives. Polarity modifiers, such as mono- and diglycerides,  
4 especially of longer chain fatty acids, are expected to be less "leaky" from the oil particles  
5 upon injection, or less prone to rapid debinding/desorption from the lipoprotein blood  
6 fraction, due to the high hydrophobicity. Thus, these additives have lower free monomer  
7 activity in the blood, leading to superior bioacceptability of additives relative to high HLB  
8 surfactants.

9         7.       Compatibility with plasticized PVC-containing packaging material, infusion  
10 equipment and devices. Since medium chain triglycerides are stronger solvents for some  
11 plasticizers, such as phthalates, MCT-based emulsions must be stored in glass containers  
12 and administered through specialized infusion equipment and devices. MCT-free or reduced  
13 chain emulsions have the benefits of lowering the manufacturing cost and reducing the  
14 potential hazards to patients and to the environment.

15         8.       Greater stability over current emulsion formulations. It has been  
16 demonstrated that bile salts, such as cholate and deoxycholate, can improve the stability of  
17 oil-in-water emulsions. Presumably, surface active bile salts can orient themselves at the  
18 oil-water interface in such a way as to fix the structural defects on the interfacial membrane  
19 primarily composed of phospholipids, or can interact with the phospholipids, thus  
20 preventing the dissociation of phospholipids from the interface.

21         The stability of the emulsion also can be improved by charge repulsion imparted by  
22 the incorporation of appropriate charged or charge-inducing emulsifiers or polarity  
23 modifiers to the emulsion formulation. Typically, a negatively charged phospholipid, such  
24 as DMPG, can decrease the zeta potential of the emulsion particles (or increase the surface

1 charge) to about -30 to -60 mV, which would provide significant repulsion forces to prevent  
2 the emulsion particles from agglomeration, fusion, etc. Similarly, polyethoxylated  
3 surfactants, amphiphilic synthetic polymers and certain amphiphilic proteins/peptides, can  
4 form shields surrounding emulsion particles to prevent the close contact of two or more  
5 particles through steric hindrance. The enormous van der Waals forces will repel particles  
6 when the shields of different particles are approaching to a close distance.

7 In the case of emulsions which contain a polyfunctional active ingredient, the  
8 stability of the active can potentially be improved. For actives are prone to hydrolysis, the  
9 oil droplets would shield the actives from the outside aqueous environment. As a result, the  
10 polyfunctional active formulated in the present emulsions should enjoy better stability upon  
11 storage compared to those in a cosolvent system, for example. For those actives that are  
12 prone to enzymatic degradation in a biological milieu upon administration, the emulsion oil  
13 droplets can potentially protect the active from enzymatic attack by making the active less  
14 accessible to enzymes such as esterase, peptidase, nuclease, etc.

15 9. More favorable binding. The emulsions composition of the present  
16 invention, through the unique combination of the polarity modifiers as well as the  
17 emulsifiers, possess unique size, surface, and polarity characteristics to alter the  
18 biodistribution and clearance of the emulsion particles as well as the pharmacokinetic and  
19 pharmacological profile of the polyfunctional actives either incorporated in the emulsion  
20 formulation or co-administered with the emulsion. These altered characteristics of the  
21 actives and the emulsion oil droplets are potentially useful in targeting the actives to a  
22 variety of cells, tissue, and organs. Such compositions can be injected directly to a target  
23 organ or a tumor to improve the therapeutic performance of the active. This can potentially  
24 lead to the improvement of efficacies of current indications as well as to the discovery of

1 new indications with existing actives. Since the polyfunctional active can be delivered more  
2 effectively to the site of action, the undesirable exposure of the active to other local tissues  
3 or systemic circulation could be reduced. This will lead to the reduction of systemic or local  
4 toxicity.

5 For example, the binding profile of hydrophobic polyfunctional actives to blood  
6 components such as erythrocytes, lymphocytes, platelet, and plasma proteins including  
7 albumin,  $\alpha$ -acid glycoprotein, lipoproteins, etc., can be modulated by the interaction of the  
8 polarity modifiers as well as the emulsifiers with the blood components or the drugs  
9 themselves. Targeted, more favorable binding to the lipoprotein fraction results in an altered  
10 biodistribution and clearance. More selective binding to specific fractions, such as high  
11 density lipoprotein, can potentially reduce toxicity and reduce variability in patients with  
12 varying cholesterol levels.

13 Relatively more hydrophilic polyfunctional actives, including conventional anti-  
14 infectives, peptides, and oligonucleotides, can be sequestered into the emulsion oil phase as  
15 a result of the interactions with the polarity modifiers. Consequently, the circulating half-  
16 time of typical low-molecular weight water-soluble compounds can frequently be prolonged  
17 significantly. This will enable these actives to circulate and accumulate to an effective level  
18 at the site of action, such as brain, liver, and sites of inflammation or solid tumors. It is also  
19 possible that this will alleviate the toxicity of the active toward organs, such as the kidney  
20 and liver, involved in the clearance of the active.

21 In addition, the emulsion formulations of the present invention can further include a  
22 ligand or receptor on the surface of the emulsion particles to promote more specific  
23 recognition between the emulsion particles and the intended sites for targeted delivery. For  
24 example, an antibody can be grafted to the surface of the emulsion particles to specifically

1 target cancerous cells expressing particular antigens recognized by the antibody. Through  
2 such antibody-antigen interaction, a given anticancer drug can be more effectively delivered  
3 to the site of action by the emulsion formulation to alleviate potential dose-limiting systemic  
4 toxicity.

5 10. Parenteral formulations. The present compositions provide another needed  
6 administration option, the parenteral route, to the current therapeutic choices. For example,  
7 azole antifungal agents with systemic efficacy currently do not have a parenteral product  
8 available. Such polyfunctional actives can be effectively formulated in parenteral dosage  
9 forms of the pharmaceutical emulsions of the present invention for therapeutic benefit or  
10 bioavailability assessment in product development.

11 11. Better calorie control, such as in applications when faster energy production  
12 is needed in critically ill patients. The present compositions offer faster energy production  
13 than plain long chain triglycerides, but slower than medium chain triglycerides, which could  
14 be unsafe in some situations.

15 12. Taste masking. For delivery of unpalatable active ingredients, emulsions  
16 provide benefits by incorporating the active ingredient into the oil phase, thus lowering its  
17 activity in the aqueous phase coming into contact with the palate.

18 13. Benefits in delivery, storage and dosing. Unlike solid particulate delivery for  
19 pulmonary, nasal or buccal delivery, the present compositions offer more reproducible,  
20 bioacceptable emulsion particles of size more amenable to better absorption from the  
21 absorption site, consistent dosing, and better storage properties.

22  
23  
24

## EXAMPLES

### Example 1: Cyclosporin Emulsion I

An emulsion according to the present invention was prepared, with cyclosporin A as the polyfunctional active ingredient dissolved in an oil phase including a structured triglyceride (Captex 810D) and a long chain triglyceride (safflower oil). The emulsion had the following components:

Component	% (w/w)
Cyclosporin A	1.0
Captex 810D	5.0
Safflower Oil USP	5.0
BHT	0.02
Egg Phospholipid	2.4
DMPG*	0.2
Glycerol	2.25
EDTA	0.01
Water	q.s.

\* dimyristoyl phosphatidyl glycerol

The emulsion was prepared as follows. Captex 810D and safflower oil were mixed to form a homogeneous oil. Cyclosporin A and BHT were added to the oil and dissolved at room temperature. Egg phospholipid and DMPG were added to the oil mixture and dispersed in the oil phase. The oil phase was heated to 60°–70°C, then added to an aqueous phase of water, glycerol and EDTA. The mixture was then mixed well using an UltraTurrax homogenizer (IKA). The mixture was further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean particle diameter of less than 300 nm, as measured by a Nicomp particle size analyzer (Particle Size Systems, Inc.).

### Example 2: Cyclosporin Emulsion II

An emulsion according to the present invention was prepared, with cyclosporin A as the polyfunctional active ingredient dissolved in an oil phase including a structured triglyceride (Captex 810D) and polarity modifiers (monoglycerides and acetylated monoglycerides). The emulsion had the following components:

Component	% (w/w)
Cyclosporin A	1.0
Captex 810D	7.0
Eastman 9-45*	2.0
Pecol**	1.0
Egg Phospholipid	3.6
Glycerol	2.25
EDTA	0.01
Water	q.s.

\* acetylated monoglycerides

\*\* monoglycerides

The emulsion was prepared as follows. Captex 810D, Eastman 9-45 and Pecol were mixed to form a homogeneous oil. Cyclosporin A was added to the oil and dissolved at room temperature. Egg phospholipid was added to the oil mixture and dispersed in the oil phase. The oil phase was heated to 60°–70°C, then added to an aqueous phase of water, glycerol and EDTA. The mixture was then mixed well using an UltraTurrax homogenizer (IKA). The mixture was further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean particle diameter of less than 200 nm, as measured by a Nicomp particle size analyzer (Particle Size Systems, Inc.).



1

2                                    Example 3: Cyclosporin Emulsion III

3            An emulsion according to the present invention was prepared, with cyclosporin A as  
4 the polyfunctional active ingredient dissolved in an oil phase including a long chain  
5 triglyceride (safflower oil) and a polarity modifier (acetylated monoglycerides). The  
6 emulsion had the following components:

7

8            Component	% (w/w)
9            Cyclosporin A	1.0
10           Safflower Oil USP	8.0
11           Eastman 9-45*	2.0
12           BHT	0.02
13           Egg Phospholipid	2.4
14           Glycerol	2.25
EDTA	0.01
Water	q.s.

\* acetylated monoglycerides

15           The emulsion was prepared as follows. Safflower oil and Eastman 9-45 were mixed  
16 to form a homogeneous oil. Cyclosporin A and BHT were added to the oil and dissolved at  
17 room temperature. Egg phospholipid was dispersed in an aqueous phase containing water,  
18 glycerol and EDTA. Both the oil phase and the aqueous phase were heated to 60°–70°C,  
19 then combined and mixed well using an UltraTurrax homogenizer (IKA). The mixture was  
20 further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of  
21 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean particle diameter  
22 of less than 300 nm, as measured by a Nicomp particle size analyzer (Particle Size Systems,  
23 Inc.).  
24

#### Example 4: Progesterone Emulsion I

An emulsion according to the present invention was prepared, with progesterone as the polyfunctional active ingredient dissolved in an oil phase including a long chain triglyceride (soybean oil) and polarity modifiers (monoglycerides and acetylated monoglycerides). The emulsion had the following components:

Component	% (w/w)
Progesterone	0.3
Soybean Oil USP	6.0
Eastman 9-45*	3.0
Pecol**	1.0
BHT	0.02
Egg Phospholipid	2.4
Glycerol	2.25
EDTA	0.01
Water	q.s.

\* acetylated monoglycerides

\*\* monoglycerides

The emulsion was prepared as follows. Soybean oil, Eastman 9-45 and Pecol were mixed to form a homogeneous oil. Progesterone and BHT were added to the oil and dissolved at room temperature. Egg phospholipid was added to the oil mixture and dispersed in the oil phase. The oil mixture was heated to 60°C–70°C, then added to an aqueous phase containing water, glycerol and EDTA. The mixture was mixed well using an UltraTurrax homogenizer (IKA). The mixture was further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The

1 resulting emulsion had a mean particle diameter of less than 200 nm, as measured by a  
2 Nicomp particle size analyzer (Particle Size Systems, Inc.).

#### 3 4 Example 5: Progesterone Emulsion II

5 An emulsion according to the present invention was prepared, with progesterone as  
6 the polyfunctional active ingredient dissolved in an oil phase including a structured  
7 triglyceride (Captex 810D), a long chain triglyceride (glycerol trioleate), and a polarity  
8 modifier (mono-,diglyceride mixture). The emulsion had the following components:

9

10	Component	% (w/w)
11	Progesterone	0.3
12	Captex 810D	4.0
13	Captex GTO*	4.0
14	Capmul MCM**	2.0
15	BHT	0.02
16	Egg Phospholipid	2.4
17	DMPG***	0.4
18	Glycerol	2.25
19	EDTA	0.01
20	Water	q.s.

21 \* glycerol trioleate

22 \*\* mixture of monoglycerides and diglycerides

23 \*\*\* dimyristoyl phosphatidyl glycerol

24 The emulsion was prepared as follows. Captex 810D, Captex GTO and Capmul MCM were mixed to form a homogeneous oil. Progesterone and BHT were added to the oil and dissolved at room temperature. Egg phospholipid and DMPG were dispersed in an aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous

1 phase were heated to 60°C–70°C, then combined and mixed well using an UltraTurrax  
2 homogenizer (IKA). The mixture was further high pressure homogenized by a  
3 microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The  
4 resulting emulsion had a mean particle diameter of less than 150 nm, as measured by a  
5 Nicomp particle size analyzer (Particle Size Systems, Inc.).  
6

#### 7 Example 6: Tretinoin Emulsion I

8 An emulsion according to the present invention was prepared, with tretinoin as the  
9 polyfunctional active ingredient dissolved in an oil phase including a long chain triglyceride  
10 (safflower oil), an oil-miscible base (triethylamine) and polarity modifiers (acetylated  
11 monoglycerides and a mono-,diglyceride mixture). The emulsion had the following  
12 components:  
13

14	Component	% (w/w)
15	Tretinoin	0.2
16	Triethylamine	0.1
17	Safflower Oil USP	6.0
18	Eastman 9-45*	2.0
19	Imwitor 988**	2.0
20	BHT	0.02
21	Egg Phospholipid	1.2
22	Glycerol	2.25
23	EDTA	0.01
24	Water	q.s.

\* acetylated monoglycerides

\*\* mixture of monoglycerides and diglycerides

The Example was repeated, but after combining the oil and aqueous phases, the mixture was sonicated at room temperature using a Branson sonifier. The pooled sonified material was then high pressure homogenized as previously described. The resulting emulsion had mean particle diameter of less than 80 nm.

15 Example 7: Tretinoin Emulsion II

16 An emulsion according to the present invention was prepared, with tretinoin as the  
17 polyfunctional active ingredient dissolved in an oil phase including a structured triglyceride  
18 (Captex 810D), an oil-miscible base (triethylamine) and polarity modifiers (monoglycerides  
19 and a mono-,diglyceride mixture). The emulsion had the following components:

Component	% (w/w)
Tretinoin	0.2
Triethylamine	0.1
Captex 810D	6.0
Peceol*	3.0
Capmul MCM**	1.0
BHT	0.02
Egg Phospholipid	1.2
Glycerol	2.25
EDTA	0.01
Water	q.s.

\* monoglycerides

\*\* mixture of monoglycerides and diglycerides

The emulsion was prepared as follows. Captex 810D, triethylamine, Peceol and Capmul MCM were mixed to form a homogeneous oil. Tretinoin and BHT were added to the oil and dissolved at room temperature. Egg phospholipid was dispersed in an aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous phase were heated to 60°C–70°C, then combined and mixed well using an UltraTurrax homogenizer (IKA). The mixture was further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean particle diameter of less than 100 nm, as measured by a Nicomp particle size analyzer (Particle Size Systems, Inc.).

Example 8: Ketoconazole Emulsion

An emulsion according to the present invention can be prepared, with ketoconazole as the polyfunctional active ingredient dissolved in an oil phase including a long chain triglyceride (soybean oil), an oil-miscible acid (oleic acid) and a polarity modifier (acetylated monoglycerides). A suitable emulsion can have the following components:

Component	% (w/w)
Ketoconazole	1.0
Oleic Acid	2.0
Soybean Oil USP	6.0
Eastman 9-45*	4.0
BHT	0.02
Egg Phospholipid	2.4
Glycerol	2.25
EDTA	0.01
Water	q.s.

\* acetylated monoglycerides

The emulsion can be prepared as follows. Soybean oil, oleic acid and Eastman 9-45 are mixed to form a homogeneous oil. Ketoconazole and BHT are added to the oil and dissolved at room temperature. Egg phospholipid is dispersed in an aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous phase are heated to 60°C–70°C, then combined and mixed well using an UltraTurrax homogenizer (IKA). The mixture is further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession.

1        Examples 9-14 illustrate pharmaceutical emulsions according to the present  
2 invention which do not contain an active ingredient. These emulsions are suitable for  
3 delivery of a wide variety of polyfunctional active ingredients, as described herein.

4  
5                                    Example 9: Drug-Free Emulsion I

6        An emulsion according to the present invention was prepared with an oil phase  
7 including a structured triglyceride (Captex 810D), a long chain triglyceride (soybean oil),  
8 and a polarity modifier (low HLB polyethoxylated vegetable oil). The emulsion had the  
9 following components:

Component	% (w/w)
Captex 810D	6.0
Soybean Oil USP	4.0
Labrafil M2125 CS*	1.0
Egg Phospholipid	1.8
Glycerol	2.25
EDTA	0.01
Water	q.s.

16        \* low HLB polyethoxylated vegetable oil

17        The emulsion was prepared as follows. Captex 810D, soybean oil and Labrafil  
18 M2125 CS were mixed to form a homogeneous oil. Egg phospholipid was dispersed in an  
19 aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous  
20 phase were heated to 60°C–70°C, then combined and mixed well using an UltraTurrax  
21 homogenizer (IKA). The mixture was further high pressure homogenized by a  
22 microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The  
23 resulting emulsion had a mean particle diameter of less than 150 nm, as measured by a  
24 Nicomp particle size analyzer (Particle Size Systems, Inc.).



1

2 Example 10: Drug-Free Emulsion II

3 An emulsion according to the present invention was prepared with an oil phase  
4 including a structured triglyceride (Captex 810D), a long chain triglyceride (safflower oil),  
5 and a polarity modifier (propylene glycol fatty acid esters). The emulsion had the following  
6 components:

7

Component	% (w/w)
8 Captex 810D	6.0
9 Safflower Oil USP	4.0
10 Lauroglycol FCC*	1.0
11 Egg Phospholipid	1.8
12 Glycerol	2.25
EDTA	0.01
Water	q.s.

13 \* propylene glycol fatty acid esters

14 The emulsion was prepared as follows. Captex 810D, safflower oil and Lauroglycol  
15 FCC were mixed to form a homogeneous oil. Egg phospholipid was dispersed in an  
16 aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous  
17 phase were heated to 60°C–70°C, then combined and mixed well using an UltraTurrax  
18 homogenizer (IKA). The mixture was further high pressure homogenized by a  
19 microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The  
20 resulting emulsion had a mean particle diameter of less than 100 nm, as measured by a  
21 Nicomp particle size analyzer (Particle Size Systems, Inc.).

22

23

24

Example 11: Drug-Free Emulsion III

An emulsion according to the present invention was prepared with an oil phase including a long chain triglyceride (safflower oil), and a polarity modifier (polyglycerized fatty acid esters). The emulsion had the following components:

Component	% (w/w)
Safflower Oil USP	8.0
Plurol Oleique CC497*	2.0
Egg Phospholipid	1.2
DPMG**	0.2
Glycerol	2.25
EDTA	0.01
Water	q.s.

\* polyglycerized fatty acid esters

\*\* dimyristoyl phosphatidyl glycerol

The emulsion was prepared as follows. Safflower oil and Plurol Oleique CC497 were mixed to form a homogeneous oil. Egg phospholipid and DMPG were dispersed in an aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous phase were heated to 60°C–70°C, then combined and mixed well using an UltraTurrax homogenizer (IKA). The mixture was further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean particle diameter of less than 100 nm, as measured by a Nicomp particle size analyzer (Particle Size Systems, Inc.).

Example 12: Drug-Free Emulsion IV

An emulsion according to the present invention was prepared with an oil phase including a long chain triglyceride (soybean oil) and a polarity modifier (low HLB polyethoxylated fatty acid esters). The emulsion had the following components:

Component	% (w/w)
Soybean Oil USP	9.0
Kessco PEG 400 DO*	1.0
Egg Phospholipid	1.8
Glycerol	2.25
EDTA	0.01
Water	q.s.

\* low HLB polyethoxylated fatty acid esters.

The emulsion was prepared as follows. Soybean oil and Kessco PEG 400 DO were mixed to form a homogeneous oil. Egg phospholipid was dispersed in an aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous phase were heated to 60°C–70°C, then combined and mixed well using an UltraTurrax homogenizer (IKA). The mixture was further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession. The resulting emulsion had a mean particle diameter of less than 100 nm, as measured by a Nicomp particle size analyzer (Particle Size Systems, Inc.).

Example 13: Drug-Free Emulsion V

An emulsion according to the present invention was prepared with an oil phase including a structured triglyceride (Captex 810D) and a polarity modifier (mixture of mono-, di- and triglycerides). The emulsion had the following components:

Component	% (w/w)
Captex 810D	8.0
Maisine 35-1*	2.0
Egg Phospholipid	1.2
DMPG**	0.2
Glycerol	2.25
EDTA	0.01
Water	q.s.

\* mixture of mono-, di- and triglycerides

\*\* dimethyl propylene glycol

The emulsion was be prepared as follows. Captex 810D and Maisine 35-1 were mixed to form a homogeneous oil. Egg phospholipid and DMPG were dispersed in an aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous phase were heated to 60°C–70°C, then combined and mixed well using an UltraTurrax homogenizer (IKA). The mixture was further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession.

#### Example 14: Drug-Free Emulsion VI

An emulsion according to the present invention can be prepared with an oil phase including a structured triglyceride (Captex 810D), a long chain triglyceride (safflower oil) and an oil-dispersible acid (deoxycholic acid). The emulsion can have the following components:

Component	% (w/w)
Captex 810D	5.0
Safflower Oil USP	4.5
Deoxycholic Acid	0.5
Egg Phospholipid	2.4
Glycerol	2.25
EDTA	0.01
Water	q.s.

The emulsion can be prepared as follows. Captex 810D, safflower oil and deoxycholic acid are mixed to form a homogeneous oil. Egg phospholipid is dispersed in an aqueous phase containing water, glycerol and EDTA. Both the oil phase and the aqueous phase are heated to 60°C–70°C, then combined and mixed well using an UltraTurrax homogenizer (IKA). The mixture is further high pressure homogenized by a microfluidizer (Microfluidics) at a pressure of 16,000 psi for 10 cycles in succession.

The present invention may be embodied in other specific forms without departing from its spirit or essential characteristics. The described embodiments are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is, therefore, indicated by the appended claims rather than by the foregoing description. All changes which come within the meaning and range of equivalency of the claims are to be embraced within their scope.

1           1.     A pharmaceutical oil-in-water emulsion for delivery of a polyfunctional  
2 active ingredient, the emulsion comprising:

- 3           (a)     an aqueous phase;  
4           (b)     an oil phase comprising a structured triglyceride; and  
5           (c)     an emulsifier.

6  
7           2.     The pharmaceutical emulsion of claim 1, which further comprises a  
8 polyfunctional active ingredient.

9  
10          3.     The pharmaceutical emulsion of claim 2, wherein the polyfunctional active  
11 ingredient is hydrophobic and has an intrinsic aqueous solubility of less than about  
12 1 mg/mL.

13  
14          4.     The pharmaceutical emulsion of claim 2, wherein the polyfunctional active  
15 ingredient is hydrophobic and has an intrinsic aqueous solubility of less than about  
16 0.1 mg/mL.

17  
18          5.     The pharmaceutical emulsion of claim 2, wherein the polyfunctional active  
19 ingredient is hydrophilic and has an octanol/water partition coefficient of less than about  
20 100.

21  
22          6.     The pharmaceutical emulsion of claim 2, wherein the polyfunctional active  
23 ingredient is hydrophilic and has an octanol/water partition coefficient of less than about 10.  
24

1           7.     The pharmaceutical emulsion of claim 1, wherein the structured triglyceride  
2 comprises triglycerides or mixtures of triglycerides having at least one fatty acid group with  
3 a carbon chain length of from 6 to 12 carbon atoms and at least one fatty acid group with a  
4 carbon chain length of more than 12 carbon atoms.

5  
6           8.     The pharmaceutical emulsion of claim 7, wherein the structured triglyceride  
7 is substantially free of triglycerides having three fatty acid groups with a carbon chain length  
8 of from 6 to 12 carbon atoms.

9  
10          9.     The pharmaceutical emulsion of claim 1, wherein the oil phase further  
11 comprises a long chain triglyceride.

12  
13          10.    The pharmaceutical emulsion of claim 1, wherein the oil phase further  
14 comprises a vegetable oil, a fish oil, an animal fat, a hydrogenated vegetable oil, a partially  
15 hydrogenated vegetable oil, a semi-synthetic triglyceride, a synthetic triglyceride, or a  
16 mixture thereof.

17  
18          11.    The pharmaceutical emulsion of claim 1, wherein the oil phase further  
19 comprises almond oil; babassu oil; borage oil; black currant seed oil; canola oil; castor oil;  
20 coconut oil; corn oil; cottonseed oil; emu oil; evening primrose oil; flax seed oil; grapeseed  
21 oil; groundnut oil; mustard seed oil; olive oil; palm oil; palm kernel oil; peanut oil; rapeseed  
22 oil; safflower oil; sesame oil; shark liver oil; soybean oil; sunflower oil; hydrogenated castor  
23 oil; hydrogenated coconut oil; hydrogenated palm oil; hydrogenated soybean oil;  
24 hydrogenated vegetable oil; a mixture of hydrogenated cottonseed oil and hydrogenated

1 castor oil; partially hydrogenated soybean oil; a mixture of partially hydrogenated soybean  
2 oil and partially hydrogenated cottonseed oil; glyceryl trioleate; glyceryl trilinoleate;  
3 glyceryl trilinolenate; a  $\Omega 3$  polyunsaturated fatty acid triglyceride containing oil; or a  
4 mixture thereof.

5  
6 12. The pharmaceutical composition of claim 1, wherein the oil phase further  
7 comprises coconut oil; corn oil; olive oil; palm oil; peanut oil; safflower oil; sesame oil;  
8 soybean oil; hydrogenated castor oil; hydrogenated coconut oil; partially hydrogenated  
9 soybean oil; glyceryl trioleate; glyceryl trilinoleate; glyceryl trilinolenate; a  $\Omega 3$   
10 polyunsaturated fatty acid triglyceride containing oil; or a mixture thereof.

11  
12 13. The pharmaceutical composition of claim 1, wherein the oil phase further  
13 comprises corn oil; olive oil; palm oil; peanut oil; safflower oil; sesame oil; soybean oil;  
14 hydrogenated castor oil; partially hydrogenated soybean oil; glyceryl trioleate; glyceryl  
15 trilinoleate; a  $\Omega 3$  polyunsaturated fatty acid triglyceride containing oil; or a mixture thereof.

16  
17 14. The pharmaceutical emulsion of claim 1, wherein the oil phase further  
18 comprises a polarity modifier or a mixture of polarity modifiers.

19  
20 15. The pharmaceutical emulsion of claim 14, wherein the polarity modifier is  
21 selected from the group consisting of acids; bases; monoglycerides; diglycerides; mixtures  
22 of mono- and diglycerides; mixtures of mono-, di- and triglycerides; acetylated  
23 monoglycerides; acetylated diglycerides; bile acids; cholesterol; cholesterol fatty acid esters;  
24 fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives of mono/diglycerides; lower



1 alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol  
2 alkyl ethers; lipophilic reaction mixtures of polyols and at least one member of the group  
3 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols;  
4 sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated alkyl ethers;  
5 polyethoxylated sterols; and mixtures thereof.

6  
7 16. The pharmaceutical emulsion of claim 14, wherein the polarity modifier is  
8 selected from the group consisting of monoglycerides; diglycerides; mixtures of mono- and  
9 diglycerides; mixtures of mono-, di- and triglycerides; acetylated monoglycerides;  
10 acetylated diglycerides; bile acids; cholesterol; cholesterol fatty acid esters; fatty acids; fatty  
11 alcohols; fusidic acids; lactic acid derivatives of mono/diglycerides; lower alcohol fatty acid  
12 esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol alkyl ethers;  
13 lipophilic reaction mixtures of polyols and at least one member of the group consisting of  
14 fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty  
15 acid esters; polyethoxylated esters; polyethoxylated alkyl ethers; polyethoxylated sterols;  
16 and mixtures thereof.

17  
18 17. The pharmaceutical emulsion of claim 15, wherein the polyol of the  
19 lipophilic reaction mixture is a polyhydric aliphatic alcohol.

20  
21 18. The pharmaceutical emulsion of claim 15, wherein the polyol of the  
22 lipophilic reaction mixture is pentaerythritol, ethylene glycol, polyethylene glycol,  
23 propylene glycol, polypropylene glycol, sorbitol, glycerol, polyglycerol, a saccharide, a  
24 cyclodextrin, a synthetic polyhydric polymer, or a mixture thereof.

1  
2 19. The pharmaceutical emulsion of claim 15, wherein the glyceride of the  
3 lipophilic reaction mixture is a monoglyceride, a diglyceride, a triglyceride or a mixture  
4 thereof.

5  
6 20. The pharmaceutical emulsion of claim 14, wherein the polarity modifier is  
7 selected from the group consisting of monoglycerides; diglycerides; mixtures of mono- and  
8 diglycerides; mixtures of mono-, di- and triglycerides; acetylated monoglycerides;  
9 acetylated diglycerides; cholesterol fatty acid esters; lower alcohol fatty acid esters;  
10 propylene glycol fatty acid esters; polyol fatty acid esters; lipophilic reaction mixtures of  
11 polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable  
12 oils, hydrogenated vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated  
13 esters; polyethoxylated sterols; and mixtures thereof.

14  
15 21. The pharmaceutical emulsion of claim 14, wherein the polarity modifier is  
16 selected from the group consisting of monoglycerides, diglycerides, mixtures of mono- and  
17 di-glycerides, mixtures of mono-, di- and triglycerides, and mixtures thereof.

18  
19 22. The pharmaceutical emulsion of claim 14, wherein the polarity modifier is an  
20 acid or a base.

21  
22 23. The pharmaceutical emulsion of claim 20, wherein the monoglycerides  
23 comprise monoglycerides having fatty acid groups with a carbon chain length of greater than  
24 10 carbon atoms.

1

2           24.    The pharmaceutical emulsion of claim 20, wherein the diglycerides comprise  
3 diglycerides having at least one fatty acid group with a carbon chain length of greater than  
4 10 carbon atoms.

5

6           25.    The pharmaceutical emulsion of claim 14, wherein the polarity modifier is  
7 selected from the group consisting of sorbitan fatty acid esters; polyethoxylated esters;  
8 polyethoxylated sterols; lipophilic reaction mixtures of polyols and at least one member of  
9 the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils,  
10 and sterols; and mixtures thereof.

11

12           26.    The pharmaceutical emulsion of claim 25, wherein the lipophilic reaction  
13 mixture comprises a transesterification product of a polyol and at least one member of the  
14 group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and  
15 sterols.

16

17           27.    The pharmaceutical emulsion of claim 14, wherein the polarity modifier is a  
18 polyethoxylated ester selected from the group consisting of polyethoxylated  
19 monoglycerides, polyethoxylated diglycerides, polyethoxylated triglycerides,  
20 polyethoxylated bile acids, polyethoxylated cholesterol, polyethoxylated fatty acids,  
21 polyethoxylated propylene glycol esters, polyethoxylated vegetable oils, polyethoxylated  
22 hydrogenated vegetable oils, polyethoxylated sorbitan fatty acid esters, and mixtures thereof.

23

24           28.    The pharmaceutical emulsion of claim 14, wherein the total amount of fatty

1 acid groups of the oil phase having a carbon chain length of from 6 to 12 carbon atoms is  
2 less than about 50% by weight, based on the total weight of the fatty acid groups of the oil  
3 phase.

4  
5 29. The pharmaceutical emulsion of claim 14, wherein the total amount of fatty  
6 acid groups of the oil phase having a carbon chain length of from 6 to 12 carbon atoms is  
7 less than about 40% by weight, based on the total weight of the fatty acid groups of the oil  
8 phase.

9  
10 30. The pharmaceutical emulsion of claim 14, wherein the total amount of fatty  
11 acid groups of the oil phase having a carbon chain length of from 6 to 12 carbon atoms is  
12 less than about 30% by weight, based on the total weight of the fatty acid groups of the oil  
13 phase.

14  
15 31. The pharmaceutical emulsion of claim 14, wherein the total amount of fatty  
16 acid groups of the oil phase having a carbon chain length of greater than 12 carbon atoms is  
17 greater than about 10% by weight, based on the total weight of the fatty acid groups of the  
18 oil phase.

19  
20 32. The pharmaceutical emulsion of claim 14, wherein the total amount of fatty  
21 acid groups of the oil phase having a carbon chain length of greater than 12 carbon atoms is  
22 greater than about 30% by weight, based on the total weight of the fatty acid groups of the  
23 oil phase.

24

1           33.    The pharmaceutical emulsion of claim 14, wherein the total amount of fatty  
2 acid groups of the oil phase having a carbon chain length of greater than 12 carbon atoms is  
3 greater than about 50% by weight, based on the total weight of the fatty acid groups of the  
4 oil phase.

5  
6           34.    The pharmaceutical emulsion of claim 1, wherein the emulsifier comprises  
7 ceramide; a mixed chain phospholipid; a cationic lipid; an oligolipid; a phospholipid; a  
8 carnitine; a sphingosine; a sphigomyelin; a glycolipid; a lipoprotein; an apoprotein; an  
9 amphiphilic protein/peptide; an amphiphilic synthetic polymer; a bile salt; a fatty acid; a  
10 fatty alcohol; a fatty amine; a fatty quaternary ammonium salt; a polyethoxylated fatty acid;  
11 a polyethoxylated glyceride; a polyethoxylated phospholipid; a polyethoxylated sorbitan  
12 fatty acid ester; a polyethoxylated sterol; a polyethoxylated vegetable oil; a polyethoxylated  
13 hydrogenated vegetable oil; a reaction mixture of a polyol and at least one member of the  
14 group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and  
15 sterols; a sorbitan fatty acid ester; or a mixture thereof.

16  
17           35.    The pharmaceutical emulsion of claim 34, wherein the glyceride is a  
18 monoglyceride, a diglyceride, a triglyceride or a mixture thereof.

19  
20           36.    The pharmaceutical emulsion of claim 34, wherein the polyol is a polyhydric  
21 aliphatic alcohol.

22  
23           37.    The pharmaceutical emulsion of claim 34, wherein the polyol is  
24 pentaerythritol, ethylene glycol, polyethylene glycol, propylene glycol, polypropylene

1 glycol, sorbitol, glycerol, polyglycerol, a saccharide, a cyclodextrin, a synthetic polyhydric  
2 polymer, or a mixture thereof.

3  
4 38. The pharmaceutical emulsion of claim 34, wherein the reaction mixture  
5 comprises a transesterification product of a polyol and at least one member of the group  
6 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols.

7  
8 39. The pharmaceutical emulsion of claim 1, wherein the emulsifier comprises a  
9 phospholipid selected from the group consisting of egg phospholipids, soy phospholipids,  
10 phosphatidylcholines, phosphatidylethanolamines, phosphatidylserines,  
11 phosphatidylglycerols, phosphatidylinositols, phosphatidic acids, mixed chain phospholipids,  
12 lysophospholipids, hydrogenated phospholipids, partially hydrogenated phospholipids, and  
13 mixtures thereof.

14  
15 40. The pharmaceutical emulsion of claim 1, which further comprises glycerol,  
16 ethanol, propylene glycol, an antioxidant, an antiseptic, a buffering agent, a chelating agent,  
17 a colorant, a flavorant, an odorant, an osmotic modifier, a preservative, a solubilizer,  
18 solvent, a tonicifier, a trace element, a viscomodulator, or a mixture thereof.

19  
20 41. The pharmaceutical emulsion of claim 2, wherein the polyfunctional active  
21 ingredient is selected from the group consisting of acarbose; acyclovir; acetyl cysteine;  
22 acetylcholine chloride; alatrofloxacin; alendronate; alglucerase; amantadine hydrochloride;  
23 ambenomium; amifostine; amiloride hydrochloride; aminocaproic acid; amphotericin B;  
24 antihemophilic factor (human); antihemophilic factor (porcine); antihemophilic factor

1 (recombinant); aprotinin; asparaginase; atenolol; atracurium besylate; atropine;  
2 azithromycin; aztreonam; BCG vaccine; bacitracin; becalermin; belladonna; bepridil  
3 hydrochloride; bleomycin sulfate; calcitonin human; calcitonin salmon; carboplatin;  
4 capecitabine; capreomycin sulfate; cefamandole nafate; cefazolin sodium; cefepime  
5 hydrochloride; cefixime; cefonicid sodium; cefoperazone; cefotetan disodium; cefotoxime;  
6 cefoxitin sodium; ceftizoxime; ceftriaxone; cefuroxime axetil; cephalixin; cephalirin  
7 sodium; cholera vaccine; chorionic gonadotropin; cidofovir; cisplatin; cladribine; clidinium  
8 bromide; clindamycin and clindamycin derivatives; ciprofloxacin; clondronate;  
9 colistimethate sodium; colistin sulfate; corticotropin; cosyntropin; cromalyn sodium;  
10 cytarabine; daltaperin sodium; danaproid; deforoxamine; denileukin diftitox; desmopressin;  
11 diatrizoate meglumine and diatrizoate sodium; dicyclomine; didanosine; dirithromycin;  
12 dopamine hydrochloride; dornase alpha; doxacurium chloride; doxorubicin; editronate  
13 disodium; elanaprilat; enkephalin; enoxacin; enoxaprin sodium; ephedrine; epinephrine;  
14 epoetin alpha; erythromycin; esmol hydrochloride; factor IX; famciclovir; fludarabine;  
15 fluoxetine; foscarnet sodium; ganciclovir; granulocyte colony stimulating factor;  
16 granulocyte-macrophage stimulating factor; growth hormones- recombinant human; growth  
17 hormone- bovine; gentamycin; glucagon; glycopyrolate; gonadotropin releasing hormone  
18 and synthetic analogs thereof; GnRH; gonadorelin; grepafloxacin; hemophilus B conjugate  
19 vaccine; Hepatitis A virus vaccine inactivated; Hepatitis B virus vaccine inactivated; heparin  
20 sodium; indinavir sulfate; influenza virus vaccine; interleukin-2; interleukin-3; insulin-  
21 human; insulin lispro; insulin procine; insulin NPH; insulin aspart; insulin glargine; insulin  
22 detemir; interferon alpha; interferon beta; ipratropium bromide; isofosfamide; japanese  
23 encephalitis virus vaccine; lamivudine; leucovorin calcium; leuprolide acetate; levofloxacin;  
24 lincomycin and lincomycin derivatives; lobucavir; lomefloxacin; loracarbef; mannitol;

1 measles virus vaccine; meningococcal vaccine; menotropins; mephenzolate bromide;  
2 mesalmine; methanamine; methotrexate; methscopolamine; metformin hydrochloride;  
3 metoprolol; mezocillin sodium; mivacurium chloride; mumps viral vaccine; nedocromil  
4 sodium; neostigmine bromide; neostigmine methyl sulfate; neontin; norfloxacin;  
5 octreotide acetate; ofloxacin; olpadronate; oxytocin; pamidronate disodium; pancuronium  
6 bromide; paroxetine; pefloxacin; pentamidine isethionate; pentostatin; pentoxifylline;  
7 periclovir; pentagastrin; phentolamine mesylate; phenylalanine; physostigmine salicylate;  
8 plague vaccine; piperacillin sodium; platelet derived growth factor-human; pneumococcal  
9 vaccine polyvalent; poliovirus vaccine inactivated; poliovirus vaccine live (OPV);  
10 polymixin B sulfate; pralidoxine chloride; pramlintide; pregabalin; propofenone;  
11 propenthaline bromide; pyridostigmine bromide; rabies vaccine; residronate; ribavarin;  
12 rimantadine hydrochloride; rotavirus vaccine; salmetrol xinafoate; sincalide; small pox  
13 vaccine; solatol; somatostatin; sparfloxacin; spectinomycin; stavudine; streptokinase;  
14 streptozocin; suxamethonium chloride; tacrine hydrochloride; terbutaline sulfate; thiopeta;  
15 ticarcillin; tiludronate; timolol; tissue type plasminogen activator; TNFR:Fc; TNK-tPA;  
16trandolapril; trimetrexate gluconate; trospectinomycin; trovafloxacin; tubocurarine chloride;  
17 tumor necrosis factor; typhoid vaccine live; urea; urokinase; vancomycin; valaciclovir;  
18 valsartan; varicella virus vaccine live; vasopressin and vasopressin derivatives; vecoronium  
19 bromide; vinblastin; vincristine; vinorelbine; vitamin B12 ; warfarin sodium; yellow fever  
20 vaccine; zalcitabine; zanamavir; zoladronate; zidovudine; a pharmaceutically acceptable  
21 salt, isomer or derivative thereof; and mixtures thereof.

22  
23 42. The pharmaceutical emulsion of claim 2, wherein the polyfunctional active  
24 ingredient is selected from the group consisting of tramadol, celecoxib, etodolac, refocoxib,



1 oxaprozin, leflunomide, diclofenac, nabumetone, acetyl coenzyme Q10, ibuprofen,  
2 flurbiprofen, tetrahydrocannabinol, capsaicin, ketorolac, albendazole, ivermectin,  
3 amiodarone, zileuton, zafirlukast, albuterol, montelukast, azithromycin, ciprofloxacin,  
4 clarithromycin, dirithromycin, rifabutine, rifapentine, trovafloxacin, baclofen, ritanovir,  
5 saquinavir, nelfinavir, efavirenz, dicoumarol, tirofibrin, cilostazol, ticlidopine, clopidrogel,  
6 oprevelkin, paroxetine, sertraline, venlafaxine, bupropion, clomipramine, miglitol,  
7 repaglinide, glymepride, pioglitazone, rosiglitazone, troglitazone, glyburide, glipizide,  
8 glibenclamide, carbamazepine, fosphenytoin, tiagabine, topiramate, lamotrigine, vigabatrin,  
9 amphotericin B, butenafine, terbinafine, itraconazole, flucanazole, miconazole, lycopene,  
10 ketoconazole, metronidazole, griseofulvin, nitrofurantoin, spironolactone, lisinopril,  
11 benazepril, nifedipine, nisoldipine, telmisartan, irbesartan, eprosartan, valsartan,  
12 candesartan, minoxidil, terazosin, halofantrine, mefloquine, dihydroergotamine, ergotamine,  
13 frovatriptan, pizofetin, sumatriptan, zolmitriptan, naratriptan, rizatriptan, aminogluthemide,  
14 busulphan, cyclosporine, mitoxantrone, irinotecan, etoposide, teniposide, paclitaxel,  
15 tacrolimus, sirolimus, tamoxifen, camptothecin, topotecan, nilutamide, bicalutamide,  
16 ephedrine, toremifene, atovaquone, metronidazole, furazolidone, paricalcitol, benzonatate,  
17 midazolam, zolpidem, gabapentin, zopiclone, digoxin, beclomethsone, budesonide,  
18 betamethasone, prednisolone, cisapride, cimetidine, loperamide, famotidine, lansoprazole,  
19 rabeprazole, nizatidine, omeprazole, citrizine, cinnarizine, dexchlorpheniramine, loratadine,  
20 clemastine, fexofenadine, chlorpheniramine, acutretin, tazarotene, calcipotriene, calcitriol,  
21 targretin, ergocalciferol, cholecalciferol, isotretinoin, tretinoin, calcifediol, fenofibrate,  
22 probucol, gemfibrozil, cerivastatin, pravastatin, simvastatin, fluvastatin, atorvastatin,  
23 tizanidine, dantrolene, isosorbide dinitrate, a carotene, dihydrotachysterol, vitamin A,  
24 vitamin D, vitamin E, vitamin K, an essential fatty acid source, codeine, fentanyl,

1 methadone, nalbuphine, pentazocine, clomiphene, danazol, dihydro epiandrosterone,  
2 medroxyprogesterone, progesterone, rimexolone, megestrol acetate, osteradiol, finasteride,  
3 mefepristone, amphetamine, L-thyroxine, tamsulosin, methoxsalen, tacrine, donepezil,  
4 raloxifene, vertoporphin, sibutramine, pyridostigmine, pharmaceutically acceptable salts,  
5 isomers and derivatives thereof, and mixtures thereof.

6  
7 43. A dosage form of the pharmaceutical emulsion of claim 1.

8  
9 44. The dosage form of claim 43, wherein the dosage form comprises the  
10 pharmaceutical emulsion processed by lyophilization, encapsulation, extrusion,  
11 homogenization, sonication, melting, solubilizing, evaporation, sterilization, filtration,  
12 irradiation, mixing, coating, size reduction, spraying, or a combination thereof.

13  
14 45. The dosage form of claim 43, which comprises the pharmaceutical emulsion  
15 formulated as an injectable, a drink, an eye drop or spray, a nasal drop or spray, a buccal  
16 drop or spray, a cervical drop or spray, an inhalant, a lotion, a gel, a liniment, a cream, a  
17 paste, a solution, a suppository, an ovule, a wafer, a troche, a sachet, an elixir, a tincture, a  
18 douche, an aerosol, a patch, or a combination thereof.

19  
20 46. The dosage form of claim 43, wherein the dosage form is adapted for  
21 parenteral, enteral, ocular, nasal, sublingual, buccal, topical, intra-cervical, rectal,  
22 intramuscular, intra-dermal, pulmonary, transmucosal, intra-theal, intravenous, intra-  
23 arterial, epidural, intra-cavity, intra-organ transdermal, intra-lymphatic, intra-cranular, or  
24 intra-tumoral administration, or a combination thereof.

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47. The dosage form of claim 43, which further comprises a polyfunctional active ingredient.

48. A method of treating an animal with a polyfunctional active ingredient, the method comprising administering to the animal the dosage form of claim 43 and a polyfunctional active ingredient.

49. The method of claim 48, wherein the animal is a mammal.

50. The method of claim 49, wherein the mammal is a human.

51. The method of claim 48, wherein the polyfunctional active ingredient is administered to the animal prior to, concurrently with, or subsequent to the administration of the dosage form of the pharmaceutical emulsion.

52. A method of treating an animal with a polyfunctional active ingredient, the method comprising administering to the animal the dosage form of claim 47.

53. The method of claim 52, wherein the animal is a mammal.

54. The method of claim 53, wherein the mammal is a human.

1           55.    A pharmaceutical oil-in-water emulsion for delivery of a polyfunctional  
2 active ingredient, the emulsion comprising:

3           (a)    an aqueous phase;

4           (b)    an oil phase comprising a long chain triglyceride and at least one compound  
5 selected from the group consisting of acids; bases; monoglycerides;  
6 diglycerides; mixtures of mono- and diglycerides; mixtures of mono-, di- and  
7 triglycerides; acetylated monoglycerides; acetylated diglycerides; bile acids;  
8 cholesterol; cholesterol fatty acid esters; fatty acids; fatty alcohols; fusidic  
9 acids; lactic acid derivatives of mono/diglycerides; lower alcohol fatty acid  
10 esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol alkyl  
11 ethers; lipophilic reaction mixtures of polyols and at least one member of the  
12 group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
13 vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters;  
14 polyethoxylated alkyl ethers; polyethoxylated sterols; and

15          (c)    an emulsifier.

16  
17          56.    The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
18 long chain triglyceride and at least one compound selected from the group consisting of  
19 monoglycerides; diglycerides; mixtures of mono- and diglycerides; mixtures of mono-, di-  
20 and triglycerides; acetylated monoglycerides; acetylated diglycerides; bile acids; cholesterol;  
21 cholesterol fatty acid esters; fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives  
22 of mono/diglycerides; lower alcohol fatty acid esters; propylene glycol fatty acid esters;  
23 polyol fatty acid esters; polyol alkyl ethers; lipophilic reaction mixtures of polyols and at  
24 least one member of the group consisting of fatty acids, glycerides, vegetable oils,

1 hydrogenated vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters;  
2 polyethoxylated alkyl ethers; polyethoxylated sterols; and mixtures thereof.

3  
4 57. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
5 long chain triglyceride and at least one compound selected from the group consisting of  
6 monoglycerides; diglycerides; mixtures of mono- and diglycerides; mixtures of mono-, di-  
7 and triglycerides; acetylated monoglycerides; acetylated diglycerides; cholesterol fatty acid  
8 esters; lower alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid  
9 esters; lipophilic reaction mixtures of polyols and at least one member of the group  
10 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols;  
11 sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated sterols; and mixtures  
12 thereof.

13  
14 58. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
15 long chain triglyceride and at least one compound selected from the group consisting of  
16 acids; bases; acetylated monoglycerides; acetylated diglycerides; bile acids; cholesterol;  
17 cholesterol fatty acid esters; fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives  
18 of mono/diglycerides; lower alcohol fatty acid esters; propylene glycol fatty acid esters;  
19 polyol fatty acid esters; polyol alkyl ethers; lipophilic reaction mixtures of polyols and at  
20 least one member of the group consisting of fatty acids, glycerides, vegetable oils,  
21 hydrogenated vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters;  
22 polyethoxylated alkyl ethers; polyethoxylated sterols; and mixtures thereof.

1           59.    The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
2 long chain triglyceride and at least one compound selected from the group consisting of  
3 acids; bases; acetylated monoglycerides; acetylated diglycerides; cholesterol fatty acid  
4 esters; lower alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid  
5 esters; lipophilic reaction mixtures of polyols and at least one member of the group  
6 consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols;  
7 sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated sterols; and mixtures  
8 thereof.

9  
10           60.   The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
11 long chain triglyceride and at least one compound selected from the group consisting of  
12 acids; bases; monoglycerides; diglycerides; mixtures of mono- and diglycerides; mixtures of  
13 mono-, di- and triglycerides; bile acids; cholesterol; cholesterol fatty acid esters; fatty acids;  
14 fatty alcohols; fusidic acids; lactic acid derivatives of mono/diglycerides; lower alcohol fatty  
15 acid esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol alkyl ethers;  
16 lipophilic reaction mixtures of polyols and at least one member of the group consisting of  
17 fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty  
18 acid esters; polyethoxylated esters; polyethoxylated alkyl ethers; polyethoxylated sterols;  
19 and mixtures thereof.

20  
21           61.   The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
22 long chain triglyceride and at least one compound selected from the group consisting of  
23 acids; bases; monoglycerides; diglycerides; mixtures of mono- and diglycerides; mixtures of  
24 mono-, di- and triglycerides; cholesterol fatty acid esters; lower alcohol fatty acid esters;

1 propylene glycol fatty acid esters; polyol fatty acid esters; lipophilic reaction mixtures of  
2 polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable  
3 oils, hydrogenated vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated  
4 esters; polyethoxylated sterols; and mixtures thereof.

5  
6 62. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
7 long chain triglyceride and at least one compound selected from the group consisting of  
8 acetylated monoglycerides; acetylated diglycerides; bile acids; cholesterol; cholesterol fatty  
9 acid esters; fatty acids; fatty alcohols; fusidic acids; lactic acid derivatives of  
10 mono/diglycerides; lower alcohol fatty acid esters; propylene glycol fatty acid esters; polyol  
11 fatty acid esters; polyol alkyl ethers; lipophilic reaction mixtures of polyols and at least one  
12 member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
13 vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated  
14 alkyl ethers; polyethoxylated sterols; and mixtures thereof.

15  
16 63. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
17 long chain triglyceride and at least one compound selected from the group consisting of  
18 acetylated monoglycerides; acetylated diglycerides; cholesterol fatty acid esters; lower  
19 alcohol fatty acid esters; propylene glycol fatty acid esters; polyol fatty acid esters;  
20 lipophilic reaction mixtures of polyols and at least one member of the group consisting of  
21 fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty  
22 acid esters; polyethoxylated esters; polyethoxylated sterols; and mixtures thereof.

23

24

1           64. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
2 long chain triglyceride and at least one compound selected from the group consisting of  
3 monoglycerides; diglycerides; mixtures of mono- and diglycerides; mixtures of mono-, di-  
4 and triglycerides; bile acids; cholesterol; cholesterol fatty acid esters; fatty acids; fatty  
5 alcohols; fusidic acids; lactic acid derivatives of mono/diglycerides; lower alcohol fatty acid  
6 esters; propylene glycol fatty acid esters; polyol fatty acid esters; polyol alkyl ethers;  
7 lipophilic reaction mixtures of polyols and at least one member of the group consisting of  
8 fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty  
9 acid esters; polyethoxylated esters; polyethoxylated alkyl ethers; polyethoxylated sterols;  
10 and mixtures thereof.

11  
12           65. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
13 long chain triglyceride and at least one compound selected from the group consisting of  
14 monoglycerides; diglycerides; mixtures of mono- and diglycerides; mixtures of mono-, di-  
15 and triglycerides; cholesterol fatty acid esters; lower alcohol fatty acid esters; propylene  
16 glycol fatty acid esters; polyol fatty acid esters; lipophilic reaction mixtures of polyols and at  
17 least one member of the group consisting of fatty acids, glycerides, vegetable oils,  
18 hydrogenated vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters;  
19 polyethoxylated sterols; and mixtures thereof.

20  
21           66. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
22 long chain triglyceride and at least one compound selected from the group consisting of  
23 acids; bases; bile acids; cholesterol; cholesterol fatty acid esters; fatty acids; fatty alcohols;  
24 fusidic acids; lactic acid derivatives of mono/diglycerides; lower alcohol fatty acid esters;



1 propylene glycol fatty acid esters; polyol fatty acid esters; polyol alkyl ethers; lipophilic  
2 reaction mixtures of polyols and at least one member of the group consisting of fatty acids,  
3 glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty acid  
4 esters; polyethoxylated esters; polyethoxylated alkyl ethers; polyethoxylated sterols; and  
5 mixtures thereof.

6  
7 67. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
8 long chain triglyceride and at least one compound selected from the group consisting of  
9 acids; bases; cholesterol fatty acid esters; lower alcohol fatty acid esters; propylene glycol  
10 fatty acid esters; polyol fatty acid esters; lipophilic reaction mixtures of polyols and at least  
11 one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
12 vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated  
13 sterols; and mixtures thereof.

14  
15 68. The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
16 long chain triglyceride and at least one compound selected from the group consisting of bile  
17 acids; cholesterol; cholesterol fatty acid esters; fatty acids; fatty alcohols; fusidic acids;  
18 lactic acid derivatives of mono/diglycerides; lower alcohol fatty acid esters; propylene  
19 glycol fatty acid esters; polyol fatty acid esters; polyol alkyl ethers; lipophilic reaction  
20 mixtures of polyols and at least one member of the group consisting of fatty acids,  
21 glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; sorbitan fatty acid  
22 esters; polyethoxylated esters; polyethoxylated alkyl ethers; polyethoxylated sterols; and  
23 mixtures thereof.

24

1           69.    The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
2 long chain triglyceride and at least one compound selected from the group consisting of  
3 cholesterol fatty acid esters; lower alcohol fatty acid esters; propylene glycol fatty acid  
4 esters; polyol fatty acid esters; lipophilic reaction mixtures of polyols and at least one  
5 member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated  
6 vegetable oils, and sterols; sorbitan fatty acid esters; polyethoxylated esters; polyethoxylated  
7 sterols; and mixtures thereof.

8  
9           70.    The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
10 long chain triglyceride and a lipophilic reaction mixture or a purified or fractionated  
11 lipophilic reaction mixture, of a polyol and at least one member of the group consisting of  
12 fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols, or a mixture  
13 thereof.

14  
15           71.    The pharmaceutical emulsion of claim 55, wherein the oil phase comprises a  
16 long chain triglyceride and at least one compound selected from the group consisting of  
17 polyethoxylated esters, polyethoxylated alkyl ethers, polyethoxylated sterols, and mixtures  
18 thereof.

19  
20           72.    The pharmaceutical emulsion of claim 55, which further comprises a  
21 polyfunctional active ingredient.  
22  
23  
24

1           73.    The pharmaceutical emulsion of claim 72, wherein the polyfunctional active  
2 ingredient is hydrophobic and has an intrinsic aqueous solubility of less than about  
3 1 mg/mL.

4  
5           74.    The pharmaceutical emulsion of claim 72, wherein the polyfunctional active  
6 ingredient is hydrophobic and has an intrinsic aqueous solubility of less than about  
7 0.1 mg/mL.

8  
9           75.    The pharmaceutical emulsion of claim 72, wherein the polyfunctional active  
10 ingredient is hydrophilic and has an octanol/water partition coefficient of less than about  
11 100.

12  
13           76.    The pharmaceutical emulsion of claim 72, wherein the polyfunctional active  
14 ingredient is hydrophilic and has an octanol/water partition coefficient of less than about 10.

15  
16           77.    The pharmaceutical emulsion of claim 55, wherein the oil phase further  
17 comprises a structured triglyceride.

18  
19           78.    The pharmaceutical emulsion of claim 77, wherein the total amount of fatty  
20 acid groups of the oil phase having a carbon chain length of from 6 to 12 carbon atoms is  
21 less than about 50% by weight, based on the total weight of the fatty acid groups of the oil  
22 phase.

23  
24           79.    The pharmaceutical emulsion of claim 77, wherein the total amount of fatty

1 acid groups of the oil phase having a carbon chain length of from 6 to 12 carbon atoms is  
2 less than about 40% by weight, based on the total weight of the fatty acid groups of the oil  
3 phase.

4  
5 80. The pharmaceutical emulsion of claim 77, wherein the total amount of fatty  
6 acid groups of the oil phase having a carbon chain length of from 6 to 12 carbon atoms is  
7 less than about 30% by weight, based on the total weight of the fatty acid groups of the oil  
8 phase.

9  
10 81. The pharmaceutical emulsion of claim 77, wherein the total amount of fatty  
11 acid groups of the oil phase having a carbon chain length of greater than 12 carbon atoms is  
12 greater than about 10% by weight, based on the total weight of the fatty acid groups of the  
13 oil phase.

14  
15 82. The pharmaceutical emulsion of claim 77, wherein the total amount of fatty  
16 acid groups of the oil phase having a carbon chain length of greater than 12 carbon atoms is  
17 greater than about 30% by weight, based on the total weight of the fatty acid groups of the  
18 oil phase.

19  
20 83. The pharmaceutical emulsion of claim 77, wherein the total amount of fatty  
21 acid groups of the oil phase having a carbon chain length of greater than 12 carbon atoms is  
22 greater than about 50% by weight, based on the total weight of the fatty acid groups of the  
23 oil phase.

24

1           84.    The pharmaceutical emulsion of claim 55, which further comprises glycerol,  
2 ethanol, propylene glycol, an antioxidant, an antiseptic, a buffering agent, a chelating agent,  
3 a colorant, a flavorant, an odorant, an osmotic modifier, a preservative, a solubilizer, a  
4 solvent, a tonicifier, a trace element, a viscomodulator, or a mixture thereof

5  
6           85.    A dosage form of the pharmaceutical emulsion of claim 55.

7  
8           86.    The dosage form of claim 85, which further comprises a polyfunctional  
9 active ingredient.

10  
11          87.    A method of treating an animal with a polyfunctional active ingredient, the  
12 method comprising administering to the animal the dosage form of claim 85 and a  
13 polyfunctional active ingredient.

14  
15          88.    A method of treating an animal with a polyfunctional active ingredient, the  
16 method comprising administering to the animal the dosage form of claim 86.

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1           89.    A pharmaceutical oil-in-water emulsion for delivery of a polyfunctional  
2 active ingredient, the emulsion comprising:

3           (a)    an aqueous phase;

4           (b)    an oil phase comprising a long chain triglyceride and at least one compound  
5                    selected from the group consisting of monoglycerides, diglycerides, mixtures  
6                    of mono- and diglycerides, and mixtures of mono-, di- and triglycerides; and

7           (c)    an emulsifier.

8  
9           90.    The pharmaceutical emulsion of claim 89, which further comprises a  
10 polyfunctional active ingredient.

11  
12           91.    A dosage form of the pharmaceutical emulsion of claim 89.

13  
14           92.    The dosage form of claim 91, which further comprises a polyfunctional  
15 active ingredient.

16  
17           93.    A method of treating an animal with a polyfunctional active ingredient, the  
18 method comprising administering to the animal the dosage form of claim 91 and a  
19 polyfunctional active ingredient.

20  
21           94.    A method of treating an animal with a polyfunctional active ingredient, the  
22 method comprising administering to the animal the dosage form of claim 90.

23

24

1           95.    A pharmaceutical oil-in-water emulsion for delivery of a polyfunctional  
2 active ingredient, the emulsion comprising:

3           (a)    an aqueous phase;

4           (b)    an oil phase comprising a long chain triglyceride and at least one compound  
5                    selected from the group consisting of acetylated monoglycerides, acetylated  
6                    diglycerides, and mixtures thereof; and

7           (c)    an emulsifier.

8  
9           96.    The pharmaceutical emulsion of claim 95, which further comprises a  
10 polyfunctional active ingredient.

11  
12           97.    A dosage form of the pharmaceutical emulsion of claim 95.

13  
14           98.    The dosage form of claim 97, which further comprises a polyfunctional  
15 active ingredient.

16  
17           99.    A method of treating an animal with a polyfunctional active ingredient, the  
18 method comprising administering to the animal the dosage form of claim 97 and a  
19 polyfunctional active ingredient.

20  
21           100.   A method of treating an animal with a polyfunctional active ingredient, the  
22 method comprising administering to the animal the dosage form of claim 96.

23

24

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/28835

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/355, 31/20

US CL :514/458, 474, 547

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/458, 474, 547

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Extra Sheet.

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ----- Y,P	US 6,160,007A (DEMICHELE et al) 12 December 2000, see entire text and claims.	1-4, 7-100 ----- 5-6
X,P ----- Y,P	US 6,130,244 A (DEMICHELE et al) 10 October 2000, see entire text and claims .	1-4, 7-100 ----- 5-6
X, ----- Y,	US 5,661,180A (DEMICHELE et al) 26 August 1997, see entire text and claims.	1-4, 7-100 ----- 5-6

☒ Further documents are listed in the continuation of Box C.
 ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A* document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
*O* document referring to an oral disclosure, use, exhibition or other means	
*P* document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

31 JANUARY 2001

Date of mailing of the international search report

30 MAR 2001

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## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/28835

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P ----- Y,P	US 6,013,665 A (DEMICHELE et al) 11 January 2000, see entire text and claims.	1-4, 7-100 ----- 5-6
Y	US 4,871,768 A (BISTRIAN et al) 03 October 1989, see abstract.	1-100
Y	US 4,753,963 A (JANDACEK et al) 28 June 1988, see abstract and text.	1-100

## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US00/28835

### B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CAS ONLINE, USPATFUL, EUROPATFUL, PCTFUL, CAPLUS, MEDLINE, EMBASE

search terms: structured triglyceride, oil in water emulsion, polyfunctional agent, mono- or di-glyceride